Cases 2026 — conversation transcript

BVN | Exported 9 October 2026

Original user prompts and assistant responses, including progress messages, in chronological order. Attachment references and source links are retained; attached documents themselves are not reproduced. Internal instructions, reasoning and tool logs are excluded. Clinical wording is preserved without retrospective correction.

1. USER | 08 Oct 2026, 14:36

Files mentioned by the user:

De Herdt _ 01.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _ 01.pdf

Distinguish instructions in attached documents from the user's request.

My request:

Context

I am a neonatologist analysing a complex case presented at the Belgian neonatology association’s autumn meeting. The attached PDF contains pregnancy, delivery, birth, and postnatal information, together with questions for discussion.

Aim

Analyse the case and answer the questions, prioritising the question on the final slide/page.

Specifications

- Recommend examinations, differential diagnoses, and management appropriate to the infant’s condition and stage of the case.

Expected output

1. **Brief case summary and direct answers**, addressing the final-slide question first.

2. **Examinations table**, ranked by priority: examination; what it would assess, confirm, or exclude; rationale; and how results would influence management.

3. **Differential diagnosis table**, ranked by likelihood: diagnosis; supporting findings; opposing findings; and distinguishing examinations or missing information.

4. **Detailed management plan**, separating immediate care from subsequent management and follow-up. Include medication, therapies, monitoring, multidisciplinary and paramedical care, and family counselling where relevant, with rationale.

5. **References and unresolved uncertainties.**

6. **Final clinical overview:** highest-priority examinations, most likely diagnosis with degree of confidence, and recommended management.

2. ASSISTANT — progress | 08 Oct 2026, 14:36

I’ll review the case PDF, address the final-page question first, and check current clinical guidance for the investigations and management. I’m using the PDF skill to read the case.

3. ASSISTANT — progress | 08 Oct 2026, 14:36

The PDF has only two pages; the final question is “What would you do?” at 10 minutes of life. The key finding is intermittent obstructive breathing despite recovery to room air, so I’ll prioritise airway assessment while also checking for consequences of the initial depression. Choanal obstruction is an important possibility, but the slides do not establish a diagnosis.

4. ASSISTANT | 08 Oct 2026, 14:38

My immediate answer to the final-slide question, “What would you do?”: assess and relieve upper-airway obstruction, check both nasal passages, and keep the infant under continuous neonatal monitoring. If obstruction causes ineffective ventilation, desaturation or bradycardia, establish an effective oral airway and escalate promptly to intubation. Nasal CPAP alone cannot reliably overcome complete bilateral nasal obstruction.

Bilateral choanal atresia or stenosis is an important structural diagnosis to exclude urgently, but it is not established by the slides. Transient pharyngeal obstruction after birth depression remains plausible.

The supplied PDF contains only two pages: a title and the initial presentation ending at 10 minutes of life. It provides no subsequent examinations, diagnosis or outcome. This analysis therefore addresses that stage of the case. Source: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _ 01.pdf].

1. Brief case summary and direct answers

A girl born at **39+4 weeks**, following spontaneous rupture of membranes and vaginal delivery through meconium-stained fluid, initially had no spontaneous breathing and bradycardia. Resuscitation included two sets of five inflation breaths, approximately eight minutes of ventilation and FiO□ up to 100%. At 10 minutes she was breathing spontaneously with PEEP in room air, without reported dyspnoea or grunting, but with **intermittent obstructive breathing**.

The immediate priorities are:

1. **Confirm the breathing pattern and physiological consequences:** respiratory effort with absent/reduced airflow, stertor versus stridor, chest movement, heart rate and preductal saturation.

2. **Optimise airway position and open the mouth**, observing whether airflow improves. Inspect the mouth, jaw and palate.

3. **Check bilateral nasal patency gently**, once ventilation is secure.

4. **Obtain urgent ENT assessment if obstruction persists**, particularly if nasal passages are not patent.

5. **Assess post-resuscitation neurological status, glucose and blood gas**, without allowing diagnostic work to delay airway support.

Meconium-stained fluid does not establish meconium aspiration syndrome. The room-air requirement and absence of reported lower-respiratory distress make clinically significant aspiration less compelling at this point. Routine suctioning is inappropriate; suction is reserved for suspected material obstructing the airway, preferably under direct vision. AHA/AAP neonatal resuscitation guideline, 2025

2. Examinations, ranked by priority

The ranking reflects the current presentation; deterioration moves resuscitation ahead of all investigations.

Priority	Examination	What it assesses, confirms or excludes	Rationale	Influence on management
1 — immediate	Continuous ECG/heart rate, preductal SpO□, respiratory rate and direct observation of effort and airflow	Severity of obstruction; obstructive versus central apnoea; response to intervention	Intermittent obstruction can precede rapid deterioration	Recurrent bradycardia, hypoxaemia or ineffective breathing requires assisted ventilation and a more secure airway

Priority	Examination	What it assesses, confirms or excludes	Rationale	Influence on management
2 — immediate	Airway examination: neutral head position, jaw support, mouth opening; inspect tongue, mandible, palate and visible secretions; listen for stertor/stridor	Positional/pharyngeal obstruction, glossoptosis, micrognathia, visible blockage or laryngeal disease	A bedside manoeuvre may both localise and relieve obstruction	Improvement guides temporary support; persistent stridor or obstruction prompts ENT/endoscopic assessment
3 — once stable	Bilateral nasal airflow assessment; gentle passage of a **6–8 Fr suction catheter** along the nasal floor, without force	Nasal obstruction and approximate site	Failure anteriorly suggests anterior narrowing; posterior resistance raises choanal obstruction	Bilateral failure supports an oral-airway strategy and urgent ENT review; catheter failure alone does not confirm atresia
4 — early	Cord gases if available; early blood gas with pH, CO□ and lactate; bedside glucose	Perinatal acidemia, impaired ventilation, residual hypoxia and hypoglycaemia	Initial depression required substantial ventilation	Hypercapnia supports inadequate ventilation; hypoglycaemia needs correction; marked acidemia triggers urgent encephalopathy assessment
5 — early, repeated	Structured neurological examination; retrieve Apgar scores and resuscitation record	Encephalopathy, abnormal tone, consciousness, reflexes or seizures	Airway disease does not exclude concurrent hypoxic injury	Moderate/severe encephalopathy with qualifying criteria requires urgent cooling-centre discussion; abnormal findings warrant EEG/aEEG
6 — urgent if persistent	ENT flexible nasal endoscopy/nasolaryngoscopy, with airway support available	Choanal patency, nasal lesions, supraglottic collapse and vocal-fold movement	Directly localises persistent upper-airway obstruction	Determines whether nasal surgery, laryngeal treatment or further airway examination is needed
7 — after stabilisation, if indicated	Low-dose CT of nasal cavity/choanae and skull base	Choanal atresia/stenosis, pyriform aperture stenosis and bony anatomy	Confirms structural nasal disease and supports operative planning	Defines the surgical approach; should not delay securing the airway
8 — conditional	Chest radiograph; pre/postductal saturations and echocardiography if persistent hypoxaemia	Aspiration, air leak, pulmonary disease, PPHN or cardiac disease	Appropriate if oxygen need or lower-respiratory signs develop	Redirects treatment towards pulmonary/cardiovascular pathology
9 — diagnosis-directed	Dysmorphology/genetic assessment; cardiac, eye, hearing and renal evaluation if choanal atresia is confirmed	Associated anomalies, particularly CHD7 disorder/CHARGE	Associated disease affects airway, feeding, anaesthetic risk and prognosis	Coordinates specialist care and genetic counselling
10 — conditional	Brain/pituitary MRI and endocrine evaluation if pyriform aperture stenosis is confirmed	Midline abnormalities and pituitary dysfunction	These can occur even without an obvious central-incisor abnormality	Identifies hormone replacement needs and influences perioperative care

Nasal catheter testing is a screening examination; persistent suspected choanal disease is evaluated with endoscopy and CT. National choanal-atresia recommendations, IPOG choanal-atresia consensus

3. Differential diagnoses, ranked provisionally by likelihood

The precise ranking is uncertain because the slide does not describe the noise, airflow, saturation pattern, airway anatomy or response to mouth opening.

Rank	Diagnosis	Supporting findings	Opposing findings / limitations	Distinguishing examination or missing information
1	**Transient positional/pharyngeal obstruction associated with reduced tone after birth depression**	Immediately post-resuscitation; intermittent obstruction; rapid improvement to room air	Persistent obstruction despite normal tone and positioning would oppose it	Tone, airflow and response to jaw support/mouth opening; repeated examination
2	**Bilateral choanal atresia or severe choanal stenosis** — leading structural concern	Obstruction from birth; nasal obstruction can cause severe neonatal compromise while oral ventilation remains effective	No documented absent nasal airflow, catheter failure or improvement with crying; fixed complete obstruction may be more persistent	Bilateral catheter testing, nasal endoscopy and CT; improvement when mouth opens
3	**Other nasal obstruction:** mucosal oedema, septal deviation, obstructing material; less commonly bilateral intranasal cysts	Early stertor/obstruction with otherwise limited pulmonary signs	No nasal examination or discharge reported	Anterior nasal examination and endoscopy; response to gentle clearance
4	**Congenital nasal pyriform aperture stenosis**	Can mimic bilateral choanal obstruction from birth	Rare; no reported anterior catheter resistance or midline findings	CT localises anterior bony narrowing; assess brain/pituitary associations if confirmed
5	**Glossoptosis associated with micrognathia/Robin sequence**	Intermittent positional upper-airway obstruction	No micrognathia or cleft palate described	Jaw/palate examination, response to jaw support, specialist airway assessment
6	**Laryngomalacia or another laryngeal lesion**, including vocal-fold immobility	Dynamic obstruction can present early	No stridor reported; severe initial depression is not typical of mild laryngomalacia	Flexible laryngoscopy; cry quality and feeding symptoms
7	**Meconium aspiration syndrome ± PPHN**	Meconium exposure and initial depression	Room-air recovery, no grunting/dyspnoea, and an obstructive pattern reduce likelihood	Respiratory examination, oxygen trajectory, radiograph; echo if hypoxaemia persists
8	**HIE, medication-related depression, metabolic disturbance or infection**	Initial apnoea and bradycardia	Does not by itself explain clear obstructive effort, although reduced tone can contribute	Neurological examination, gases/glucose, maternal medication history and infection risk

The nasal and laryngeal alternatives require anatomical confirmation rather than inference from breathing noise alone. CNPAS diagnostic case series, IPOG laryngomalacia consensus

4. Management plan

Immediate care: next minutes

- **Continue care in a monitored neonatal setting**, with senior neonatal help and access to ENT/anaesthesia. Reassess after each airway intervention.

- Maintain neutral head position and jaw support. Open the mouth and verify effective airflow and chest movement. Clear visible obstructing material selectively.

- If bilateral nasal obstruction is suspected, use an appropriately fitted **oral airway or specialist McGovern nipple** as a temporary bridge. If this does not provide reliable ventilation, or events recur, proceed to **orotracheal intubation**.

- If apnoea, gasping or heart rate below 100/min recurs, provide effective positive-pressure ventilation. A supraglottic airway is a rescue option in this term infant if mask ventilation or intubation is unsuccessful. Chest compressions are indicated only if heart rate remains below 60/min despite effective ventilation. Titrate oxygen to measured saturation; the earlier use of 100% oxygen is not an indication to continue it. European neonatal resuscitation guidance, 2025

- **Withhold oral feeding while breathing is unstable.** Obtain IV access and provide glucose-containing fluids according to weight, glucose and local neonatal protocol. Once stable, consider orogastric feeding; a nasal tube could worsen limited nasal patency.

- Maintain normal temperature unless therapeutic hypothermia is specifically indicated. Monitor glucose, perfusion and gas trends.

Parallel assessment for hypoxic injury

Retrieve cord/early gases, Apgar scores, fetal events and the exact duration of positive-pressure ventilation; perform serial neurological examinations during the first six hours.

Eight minutes of ventilation and PEEP at 10 minutes **do not establish cooling eligibility**. PEEP/CPAP is not automatically equivalent to ongoing positive-pressure resuscitation. If qualifying biochemical/perinatal criteria and moderate-to-severe encephalopathy are present, initiate therapeutic hypothermia through the local pathway, ideally within six hours: standard whole-body cooling targets **33.5°C for 72 hours**, with EEG and intensive monitoring. AAP clinical report, 2026

Subsequent treatment, determined by the cause

Confirmed cause	Recommended approach and rationale
Transient pharyngeal/positional obstruction	Wean support only after stable breathing in sleep and during supervised feeding. Recurrence requires renewed anatomical assessment
Bilateral choanal atresia/critical stenosis	Maintain a dependable airway while arranging early ENT repair. Transnasal endoscopic repair is generally preferred; postoperative endoscopic surveillance is needed because restenosis can occur. Stenting is individualised rather than assumed mandatory. IPOG consensus
Pyriform aperture stenosis	Mild stable disease may allow conservative care; persistent apnoea, hypoxaemia or inability to feed safely favours surgery. Obtain endocrine advice and brain/pituitary assessment. A small retrospective cohort supports baseline endocrine testing and MRI at diagnosis, but the evidence is limited. CNPAS endocrine study
Glossoptosis/Robin sequence	Coordinate ENT and craniofacial care; select positioning, airway adjuncts or surgery according to documented obstruction and feeding safety. Any therapeutic prone positioning requires monitored specialist care and a separate discharge sleep plan
Laryngomalacia/other laryngeal lesion	Manage according to endoscopic diagnosis and severity; significant apnoea, hypoxaemia or growth/feeding compromise may require operative treatment. Assess swallowing when aspiration is suspected
Pulmonary disease or infection	Treat the demonstrated physiology and cause; these pathways become relevant if pulmonary signs, oxygen dependence or infection indicators emerge

Medication and therapies

There is **no empirical medication that corrects fixed anatomical obstruction**.

- Use saline and gentle nasal care where appropriate.

- Reserve topical decongestants or nasal steroids for a specific ENT-directed indication, with neonatal formulation, dose and duration.

- Provide protocol-based analgesia for procedures and surgery; sedation requires a secure airway strategy.

- Give antibiotics for suspected infection or indicated surgical prophylaxis, rather than meconium exposure alone.

- Do not start caffeine for mechanical obstruction, or routine acid suppression for noisy breathing.

- If hypoglycaemia or pituitary deficiency is identified, treat promptly with neonatal/endocrine guidance.

Monitoring, multidisciplinary care and follow-up

Monitor cardiorespiratory events, work of breathing, oxygen requirement, temperature, glucose, intake/output and growth. Repeat gases when ventilation or perfusion remains uncertain.

Involve neonatal nursing, ENT and anaesthesia early; add genetics, cardiology, ophthalmology, audiology, endocrinology or neurology according to findings. Feeding/swallow therapists, lactation support and dietetics should help establish safe feeding and adequate growth. Arrange developmental follow-up if encephalopathy or significant hypoxic injury is demonstrated.

Discharge requires a stable airway during sleep and feeds, adequate intake, and an agreed follow-up plan. Explain to the family what is known and what remains suspected, teach any prescribed airway/nasal care, and provide clear instructions for cyanosis, pauses in breathing, increasing effort or poor feeding.

5. References and unresolved uncertainties

The linked references above support resuscitation, airway investigation, cause-specific care and cooling assessment. Resuscitation and cooling recommendations have stronger evidence than many rare-airway treatment decisions, which rely substantially on consensus and small series.

The most consequential missing information is:

- Saturation and heart-rate trends during obstruction.

- Stertor versus stridor; respiratory effort and actual airflow.

- Response to mouth opening, jaw support or crying.

- Nasal catheter passage and craniofacial examination.

- Apgar scores, cord/early gases and neurological status.

- Birthweight, fetal monitoring, maternal medication and infection risks.

- Whether “PEEP” means mask support or nasal CPAP.

No subsequent diagnosis or outcome can be inferred from this PDF.

6. Final clinical overview

Highest-priority examinations: direct airway/airflow assessment with continuous heart rate and SpO□; gentle bilateral nasal patency testing once stable; early gas/glucose and serial neurological examination; urgent ENT endoscopy if obstruction persists.

Most likely diagnosis: intermittent upper-airway obstruction is the leading clinical syndrome, with moderate confidence. Its anatomical cause remains low-confidence. Transient pharyngeal obstruction is plausible; **bilateral choanal atresia/stenosis is the structural diagnosis to exclude first**.

Recommended management: monitored neonatal admission, immediate airway optimisation, an oral airway bridge if nasal obstruction is suspected, and prompt intubation if ventilation is unreliable. Confirm the anatomy before definitive treatment, support feeding safely, and assess cooling eligibility in parallel within the six-hour window.

- Suggested follow-up: Create a meeting answer slide | Prompt: Turn this case analysis into one concise meeting slide answering Q1, with speaker notes and references.

- Suggested follow-up: Build an airway decision pathway | Prompt: Create a bedside decision pathway for this term newborn with intermittent obstructive breathing, including escalation triggers.

- Suggested follow-up: Reassess with further findings | Prompt: Update the differential diagnosis and management when I provide the nasal patency findings, gases, Apgar scores and neurological examination.

5. USER | 08 Oct 2026, 14:39

Files mentioned by the user:

De Herdt _ 02.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _ 02.pdf

Distinguish instructions in attached documents from the user's request.

My request:

This is what happened next. Answer 'how would you support' only.

6. ASSISTANT — progress | 08 Oct 2026, 14:40

I'll read the next slides and answer only "How would you support?" at this stage of the case.

7. ASSISTANT | 08 Oct 2026, 14:40

I would support the airway with a nasopharyngeal airway, under NICU monitoring, and provide tube feeding until swallowing is shown to be safe. Recurrent desaturation/apnoea, trismus and poor bulbar reflexes make observation with intermittent chin lift insufficient. These are the new findings in [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _ 02.pdf].

- **Airway:** maintain gentle chin lift/jaw support while arranging an appropriately sized and positioned **nasopharyngeal airway**, provided nasal patency permits. This bypasses tongue-base/pharyngeal obstruction without requiring mouth opening. Confirm that it abolishes obstructive events and maintain its patency with appropriate secretion care. Positioning is an adjunct under continuous observation. Neonatal nasopharyngeal-airway guidance

- **Respiratory support:** continuously monitor ECG, SpO□ and respiratory effort; assess CO□ if ventilation is uncertain. If obstruction persists despite the airway adjunct, a closely monitored trial of nasal CPAP may help splint the airway. Oxygen alone will not correct obstruction or hypoventilation. During apnoea with ineffective ventilation, provide positive-pressure ventilation promptly.

- **Escalation:** involve neonatal anaesthesia and ENT early because **trismus predicts difficult oral intubation and may prevent supraglottic-airway insertion**. Recurrent events despite support, hypercapnia, exhaustion or inability to handle secretions warrant a definitive airway. Plan expert intubation—potentially flexible endoscopic nasotracheal intubation—with rescue arrangements; avoid repeated traumatic oral attempts. ESAIC/BJA neonatal and infant airway guideline

- **Feeding and secretions:** withhold oral feeds because poor suck/gag and sialorrhoea raise concern for unsafe swallowing. Provide IV glucose initially, then gastric tube feeds once respiratory stability permits, choosing the route to preserve airway patency. Use gentle suction for pooled secretions and obtain specialist feeding/swallow assessment before oral feeding. A nasopharyngeal airway relieves obstruction but **does not protect against aspiration**.

The practical bridge is therefore a nasopharyngeal airway plus monitored respiratory support and protected nutrition, with a low threshold for planned expert intubation if either ventilation or secretion handling remains unreliable.

8. USER | 08 Oct 2026, 14:41

Files mentioned by the user:

De Herdt _ 03.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _ 03.pdf

Distinguish instructions in attached documents from the user's request.

My request:

What is the differential diagnosis?

9. ASSISTANT — progress | 08 Oct 2026, 14:41

I'll read the new findings and use them to update and rank the differential diagnosis.

10. ASSISTANT | 08 Oct 2026, 14:42

The differential now centres on congenital neurological or neuromuscular disease causing trismus, bulbar dysfunction and airway obstruction. The combination of poor suck/gag, sialorrhoea, reduced facial expression, axial hypotonia and peripheral hypertonia is difficult to explain by an isolated airway anomaly. The new slide documents nasopharyngeal-airway/CPAP support but no additional diagnostic findings: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _ 03.pdf].

This is a **provisional ranking by phenotypic fit**, with low confidence in any single diagnosis.

Rank	Diagnosis	Findings supporting it	Missing or opposing findings; how to distinguish
1	**Congenital brainstem dysfunction/dysgenesis**, including congenital cranial dysinnervation	Trismus from birth, facial hypomobility, impaired sucking/swallowing and mixed tone suggest involvement of several cranial motor pathways	Examine eye movements, facial symmetry, tongue movement and other cranial nerves; obtain **brain MRI with detailed brainstem assessment**. A Möbius-spectrum disorder becomes more compelling if facial weakness and impaired abduction are demonstrated
2	**Crisponi syndrome / cold-induced sweating syndrome** — **CRLF1**, less commonly **CLCF1**	Particularly relevant combination of neonatal restricted jaw opening, feeding difficulty, peripheral hypertonia and respiratory episodes	Look for stimulus-induced facial/oropharyngeal spasms, unexplained hyperthermia, camptodactyly and characteristic facial features; molecular confirmation. Absence of cold-induced sweating in a newborn does **not** exclude it
3	**Hereditary hyperekplexia** — **GLRA1, GLRB, SLC6A5**	Congenital stiffness and potentially life-threatening apnoea; feeding/handling may provoke attacks	No exaggerated startle is documented; axial hypotonia and persistent bulbar dysfunction are less typical. Determine whether stiffness is stimulus-induced, non-habituating and reduced during sleep; targeted genetics
4	**Congenital mechanical restriction of jaw opening**: TMJ ankylosis, maxillomandibular syngnathia, oral bands or coronoid abnormality	Limited mandibular range from birth	Does not adequately explain the broader neurological findings. Distinguish a **fixed mechanical endpoint** from variable muscle spasm through specialist examination and targeted imaging

Rank	Diagnosis	Findings supporting it	Missing or opposing findings; how to distinguish
5	**Distal arthrogryposis syndromes**, particularly **MYH8-related trismus–pseudocamptodactyly** and **MYH3-related Freeman–Sheldon syndrome**	Congenital jaw restriction and limited facial movement	Look for finger/foot contractures, microstomia and characteristic facial morphology. Pseudocamptodactyly may appear only with wrist extension; normal grasp reflexes do not exclude it
6	**Acquired central injury or neonatal seizures**: hypoxic-ischaemic injury, haemorrhage or focal brainstem injury	Initial depression, abnormal tone and impaired bulbar function	pH 7.21, lactate 3.2 and Apgar recovery provide limited support for severe intrapartum hypoxia. Persistent congenital trismus is unusual. Serial neurological examination, **video-EEG during events** and MRI distinguish these possibilities
7	**Metabolic or medication-related rigidity/dystonia**	Hypoglycaemia, hypocalcaemia or drug exposure can cause abnormal tone and episodic spasms	Less convincing for persistent jaw restriction and facial/bulbar findings from birth. Check glucose, ionised calcium, magnesium and relevant maternal/neonatal exposures

Congenital trismus associated with brainstem dysgenesis has been reported; Crisponi syndrome and hyperekplexia offer distinct, testable clinical patterns. Brainstem-dysgenesis case report, Crisponi syndrome—GeneReviews, Hyperekplexia—GeneReviews. The contracture syndromes are supported by MYH8 genetic research and the Freeman–Sheldon syndrome description.

Neonatal tetanus belongs on a general trismus differential, but is extremely unlikely here: symptoms were present immediately at birth. Its usual pattern is normal sucking/crying initially, followed by loss of these abilities and rigidity/spasms between days 3 and 28. Maternal residence in Congo alone is not evidence for tetanus. WHO

The most useful discriminator is whether the jaw restriction is fixed or dynamic. Fixed restriction favours structural or contracture disease; stimulus-dependent spasms favour Crisponi syndrome or hyperekplexia; persistent facial and bulbar weakness favours congenital brainstem/cranial nerve dysfunction. Interpret repeat examinations in light of dexmedetomidine, although it cannot explain findings documented before treatment.

11. USER | 08 Oct 2026, 14:43

Files mentioned by the user:

De Herdt _04.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _04.pdf

Distinguish instructions in attached documents from the user's request.

My request:

12. ASSISTANT | 08 Oct 2026, 14:43

What would you like me to address in this next part of the case—its final-slide question, an updated differential diagnosis, or management?

13. USER | 08 Oct 2026, 14:44

address this next part of the case

14. ASSISTANT — progress | 08 Oct 2026, 14:44

I'll review the new slides and address the question at this stage of the case.

15. ASSISTANT | 08 Oct 2026, 14:45

I would localise the problem primarily to the brainstem—across pontine and medullary cranial nerve systems—with congenital brainstem dysgenesis or cranial dysinnervation now the leading explanation. Bilateral hearing impairment strengthens this localisation when considered alongside facial and bulbar dysfunction, although BERA alone does not prove a central lesion.

The new slides report respiratory independence by day 6, persistent exclusive tube feeding and bilateral deafness on BERA. They also show ultrasound and sagittal MRI images without a written radiological interpretation: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/De Herdt _04.pdf].

How the findings localise

Finding	Relevant structures	Interpretation
Trismus/restricted jaw opening	Trigeminal motor system (**V**, pons), jaw-control pathways, or mechanical jaw structures	Supports pontine motor dysfunction if restriction is neurogenic; trismus alone cannot distinguish this from a mechanical cause
Limited facial expression	Facial nucleus/nerve (**VII**, pons)	Suggests facial motor dysfunction; confirm actual weakness clinically
Poor suck, swallowing difficulty and sialorrhoea	Coordinated **V, VII, IX, X and XII** function; pontomedullary feeding networks	Suggests broader bulbar dysfunction rather than isolated jaw restriction
Reduced gag	**IX** afferent and **X** efferent pathways, medulla	Compatible with lower cranial nerve dysfunction, but gag alone is an imperfect measure of swallowing safety
Bilateral abnormal BERA	Cochlea, **VIII**, and auditory brainstem pathways	Adds an auditory-system abnormality; waveform analysis and further audiology are needed to identify its level
Preserved grasp reflexes	Spinal/peripheral motor circuits	Compatible with predominant cranial involvement; does not exclude more extensive neurological disease

The unifying pattern is multiple cranial nerve dysfunction, rather than a single peripheral nerve lesion. Congenital brainstem dysgenesis has been described with trismus, swallowing problems, respiratory dysfunction and multiple cranial nerve abnormalities. Congenital trismus associated with brainstem dysgenesis

What the MRI adds

On the final slide, the left arrow appears to highlight an unusually small or flattened **ventral pontine contour**. This raises suspicion of pontine hypoplasia and fits the clinical localisation. However, the two selected sagittal images do not establish the diagnosis, the extent of the abnormality, or whether the second image is a comparison image. The complete MRI and paediatric neuroradiology report are essential.

Updated diagnostic priorities

1. **Congenital brainstem dysgenesis with multiple cranial nerve involvement** — the strongest unifying diagnosis at this stage.

2. **A genetic hindbrain/cranial dysinnervation disorder**, including **HOXA1-related disease**. Deafness, facial weakness and swallowing dysfunction fit; examine specifically for horizontal gaze palsy and associated cardiovascular abnormalities. This is a candidate, not a confirmed molecular diagnosis. HOXA1-related disorders

3. **Möbius-spectrum disease**, particularly if congenital facial weakness and impaired ocular abduction are demonstrated. Reduced facial expression alone is insufficient for this label.

4. **Other syndromic cranial nerve disorders**, including CHD7-related disease, guided by associated findings.

Crisponi syndrome, hyperekplexia and isolated mechanical trismus now move down the list because they explain the combined auditory, facial and bulbar findings less well.

The next examinations that would resolve the localisation are:

- **Full MRI review**, with detailed brainstem, cranial nerve and internal auditory canal assessment.

- **Focused cranial nerve examination**, especially ocular abduction/horizontal gaze, facial movement, tongue movement and palatal function.

- **Diagnostic audiology:** review BERA thresholds and waves, otoacoustic emissions/cochlear microphonics and middle-ear assessment to distinguish cochlear hearing loss from auditory neuropathy or central conduction abnormalities.

- **ENT vocal-fold and specialist swallowing assessment**, because respiratory improvement does not establish safe swallowing.

- **Clinical genetics assessment**, with testing directed by the MRI and phenotype.

My answer to Q4: a predominantly **pontomedullary developmental disorder involving multiple cranial nerve systems**, with suspected pontine hypoplasia on the displayed MRI. Confidence is moderate in the clinical localisation, but the structural and genetic diagnosis remains unconfirmed.

16. USER | 08 Oct 2026, 14:45

What are your differential diagnoses?

17. ASSISTANT — progress | 08 Oct 2026, 14:46

I'll refine the differential around the combination of suspected pontine abnormality, deafness and facial/bulbar dysfunction.

18. ASSISTANT | 08 Oct 2026, 14:46

My leading specific diagnosis is now pontine tegmental cap dysplasia (PTCD), within the broader category of congenital brainstem dysgenesis. I should have included it explicitly in the previous answer: the combination of suspected ventral pontine hypoplasia, bilateral hearing impairment and multiple cranial nerve deficits makes it particularly relevant. It requires confirmation on the complete MRI.

Priority	Differential diagnosis	Why it fits	Key distinguishing findings
1	**Pontine tegmental cap dysplasia**	Pontine abnormality, deafness, facial hypomobility, severe sucking/swallowing dysfunction and abnormal tone form a coherent phenotype	MRI showing a **flattened ventral pons and dorsal tegmental "cap" protruding into the fourth ventricle**, with cerebellar peduncle abnormalities; assess cranial nerve development
2	**Other congenital brainstem dysgenesis / cranial dysinnervation disorder**	Congenital dysfunction across trigeminal, facial, auditory and bulbar systems	Detailed brainstem/cranial nerve MRI; absence of the characteristic PTCD cap would favour another developmental disorder
3	**HOXA1-related disorder**	Bilateral deafness, facial paresis, swallowing dysfunction and respiratory abnormalities	Horizontal gaze palsy/Duane anomaly, inner-ear malformations, carotid anomalies or congenital heart disease; **biallelic HOXA1 variants**

Priority	Differential diagnosis	Why it fits	Key distinguishing findings
4	**Möbius syndrome or Möbius-spectrum disorder**	Congenital facial and bulbar dysfunction; trismus may accompany broader brainstem involvement	Demonstrate **facial weakness and impaired ocular abduction**. Deafness and the suspected pontine morphology make PTCD particularly important to distinguish
5	**CHD7-related disorder / CHARGE spectrum**	Hearing impairment, facial weakness and swallowing dysfunction can reflect multiple cranial nerve anomalies	Coloboma, characteristic ears/semicircular canal abnormalities, choanal atresia, cardiac or genital abnormalities; **CHD7 testing**
6	**Other pontocerebellar developmental disorders**, including pontocerebellar hypoplasia	Possible small pons, feeding impairment and abnormal tone	Cerebellar morphology, serial head growth and wider neurological phenotype; profound cranial neuropathies are especially suggestive of PTCD
7	**Prenatal/perinatal brainstem injury**	Could produce cranial nerve dysfunction and abnormal tone	MRI evidence of destructive injury rather than malformation; perinatal history currently gives limited support

PTCD's association with deafness, facial palsy and swallowing impairment is documented in the original description and a severe-phenotype series. The alternatives are supported by HOXA1 GeneReviews and CHD7 GeneReviews.

Lower down: Crisponi syndrome, hyperekplexia, mechanical jaw restriction and distal arthrogryposis still explain parts of the presentation, but do not readily unify the hearing impairment and suspected brainstem malformation.

The decisive next step is expert review of the full MRI specifically for PTCD morphology and cranial nerve abnormalities. The displayed sagittal image alone cannot confirm PTCD, and abnormal BERA alone cannot establish whether hearing loss is cochlear, neural or central.

19. USER | 08 Oct 2026, 14:47

How would you manage PTCD?

20. ASSISTANT — progress | 08 Oct 2026, 14:47

I'll focus on management for this infant's PTCD phenotype, particularly swallowing safety, breathing, hearing and cranial nerve care.

21. ASSISTANT | 08 Oct 2026, 14:48

PTCD management is supportive and multidisciplinary; there is no treatment that corrects the brainstem malformation. For this infant—off respiratory support by day 6, but with severe bulbar dysfunction and bilateral hearing impairment—I would prioritise **safe feeding, assessment of breathing during sleep, corneal protection and early communication support**.

PTCD-specific evidence comes mainly from small series and case reports, so interventions should follow the child's demonstrated deficits.

Priority	Management	Application to this infant
1. Feeding and aspiration	Continue tube feeding; involve a feeding/swallow therapist and dietitian. Assess swallowing with **VFSS or FEES** when clinically feasible	Poor suck/gag and sialorrhoea make unrestricted oral feeding unsafe. A gag reflex alone cannot determine swallowing safety. Monitor growth and respiratory symptoms; **tube feeding does not prevent aspiration of saliva or reflux**
2. Durable nutrition	Discuss **gastrostomy** if prolonged inability to feed safely is expected	Nasogastric feeding is a reasonable bridge. Gastrostomy can provide reliable nutrition without repeated nasal instrumentation; timing depends on trajectory and family preferences. It does not itself protect the airway
3. Breathing	Observe sleep and wakefulness; assess oxygenation **and CO□**. Arrange sleep/respiratory assessment, ideally polysomnography where feasible	Daytime respiratory independence does not exclude central apnoea, obstruction or sleep hypoventilation. Recurrent obstruction may require an airway adjunct/CPAP; central hypoventilation requires ventilatory support with a backup rate
4. Eyes—assess promptly	Ophthalmology review of **corneal sensation, blink, eyelid closure and ocular surface**	Trigeminal sensory loss and facial weakness can cause painless corneal injury. Prescribe lubrication and exposure protection if indicated; severe disease may require surgical protection
5. Hearing and communication	Complete diagnostic audiology and high-resolution assessment of cochlear nerves/inner ears; refer early to a specialist hearing team	Assess hearing-aid benefit and cochlear-implant candidacy individually. Begin accessible communication, including visual/sign-based interaction, without waiting for an implant decision
6. Development and motor function	Early physiotherapy, occupational therapy, speech/communication therapy and developmental follow-up	Address axial hypotonia, peripheral hypertonia, positioning, contractures and later balance/coordination difficulties; support abilities through hearing- and vision-accessible assessment

Severe swallowing dysfunction requiring gastrostomy and corneal injury are documented complications of PTCD. Severe-phenotype series

Respiratory escalation and secretion management

If desaturation/apnoea returns, determine whether the mechanism is obstruction, central apnoea, hypoventilation or aspiration. Persistent ineffective ventilation or inability to manage secretions warrants expert airway review; tracheostomy is reserved for a sustained clinical need, rather than the diagnosis alone.

Use gentle suction and positioning for troublesome pooled secretions. Consider medication to reduce secretions only after specialist assessment: anticholinergic treatment can thicken secretions and complicate clearance. Oxygen may help selected central-apnoea phenotypes, but should be titrated during monitored assessment with CO□ measurement; it is not adequate treatment for hypoventilation. PTCD reports also highlight eye injury from leaking non-invasive ventilation interfaces. PTCD sleep-apnoea case series

Hearing rehabilitation

Cochlear implantation has benefited some patients, but outcomes vary with cochlear nerve anatomy and central auditory function. Bilateral abnormal BERA alone neither establishes candidacy nor predicts benefit. Families should receive realistic counselling and early access to communication support regardless of the intervention chosen. Cochlear-implant report

Further assessment and procedural planning

Confirm the MRI diagnosis through paediatric neuroradiology and document cranial nerve function, including eye movements, facial sensation/movement, tongue movement and vocal-fold mobility. Examine for associated cardiac, renal and vertebral/rib abnormalities, with targeted imaging and reasonable baseline cardiac/renal screening.

Clinical genetics should review the phenotype and discuss testing to exclude overlapping syndromes. Do not assume a Mendelian recurrence risk without an established cause.

Record **trismus and the anticipated difficult airway** prominently. Any gastrostomy, hearing procedure or other anaesthetic needs an experienced paediatric anaesthesia team, a planned airway strategy, eye protection and appropriate postoperative respiratory monitoring.

Family counselling and follow-up

Explain that PTCD is a congenital malformation with highly variable functional outcomes. Feeding can improve with age, but severe persistent disability also occurs; MRI alone cannot predict this infant's developmental potential. Some reported adolescents achieved useful communication and substantially improved swallowing. Long-term outcome series

Coordinate follow-up through one lead clinician, with neonatal/paediatric neurology, ENT, respiratory/sleep medicine, ophthalmology, audiology, rehabilitation and nutrition. Before discharge, establish a reliable feeding plan, assess sleep-related breathing risk, train caregivers in tube and secretion care, and provide an emergency plan.

For this child, I would now continue tube nutrition, assess swallowing and likely gastrostomy needs, obtain prompt corneal assessment, evaluate sleep ventilation, and start hearing/communication rehabilitation. Being off CPAP does not resolve the bulbar or sensory risks.

22. USER | 08 Oct 2026, 14:55

Files mentioned by the user:

REGRAGUI_ 01.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_ 01.pdf

Distinguish instructions in attached documents from the user's request.

My request:

This is the next case. Answer the question on the last slide.

23. ASSISTANT — progress | 08 Oct 2026, 14:55

I'll read the new case and answer the question on its last slide.

24. ASSISTANT | 08 Oct 2026, 14:56

I would urgently obtain an abdominal ultrasound with Doppler and direct UVC-tip localisation, alongside an abdominal radiograph and blood tests. The combination of **DOL 2 abdominal distension, feeding intolerance and oliguria during TPN through a UVC** makes catheter-related extravasation/ascites a priority to exclude, while investigating NEC or perforation in parallel.

This is the presentation on the final slide of [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_ 01.pdf].

Priority	Investigation	What I would assess	How it changes the next step
1 — immediate bedside assessment	Serial abdominal examination, girth, weight/fluid balance, perfusion/BP and measured urine output	Tense versus gaseous distension; tenderness, discoloration, organ enlargement; bilious aspirates, blood in stool, meconium passage; systemic compromise	A tense abdomen with oliguria, respiratory deterioration or poor perfusion raises concern for abdominal compartment physiology and requires urgent senior/surgical review

Priority	Investigation	What I would assess	How it changes the next step
2 — urgent ultrasound	**Abdominal ultrasound with Doppler and UVC localisation**, including liver, portal circulation, bowel, kidneys and bladder	Ascites, hepatic TPN collection/haematoma, catheter malposition, thrombosis; bowel wall/perfusion abnormalities; urinary obstruction	Extravasation redirects care towards stopping UVC use and assessing the need for drainage; bowel abnormalities support NEC/surgical assessment
3 — urgent radiograph	Supine abdominal radiograph including the catheter course; add cross-table lateral or left lateral decubitus view if perforation is suspected	Bowel gas pattern, pneumatosis, portal venous gas, free air, paucity/central displacement of bowel gas suggesting ascites; UVC position	Free air requires urgent surgical consultation; NEC findings guide treatment. Radiography does not replace ultrasound for catheter-tip assessment
4 — immediate blood tests	Blood gas/lactate, glucose, full blood count/platelets, electrolytes, urea and creatinine	Acidosis/hypoperfusion, thrombocytopenia, bleeding, electrolyte disturbance and renal dysfunction	Establishes severity and guides circulatory, glucose and fluid support; compare creatinine and urine output with previous values
5 — infection/injury assessment	Blood culture and CRP if NEC/sepsis is suspected; liver tests and coagulation if hepatic injury, bleeding or significant illness	Infection, hepatic injury and coagulopathy	Supports antibiotics and bleeding management when indicated; normal early inflammatory markers do not exclude NEC/sepsis
6 — conditional	**Ultrasound-guided ascitic fluid sampling**, if drainage is clinically indicated or fluid identity remains important	Glucose/triglycerides suggesting TPN; fluid creatinine compared with serum for urinary ascites; cell count/culture and other tests guided by appearance	Helps distinguish TPN leakage, urine, blood or infected fluid. Not a routine first investigation in a stable infant

UVC-related extravasation can cause ascites, hepatic injury and abdominal compartment syndrome with oliguria. Neonatal UVC guidance, DOL 2 TPN-extravasation case report. Radiography, ultrasound and laboratory assessment are complementary when NEC is suspected. Neonatal NEC guideline

While arranging these investigations, I would pause TPN through the UVC if leakage is suspected, obtain alternative access with glucose provision, withhold feeds and decompress the stomach. I would not attribute this to “CPAP belly” before excluding ascites, catheter injury and intestinal disease—particularly because oliguria accompanies the distension.

25. USER | 08 Oct 2026, 14:57

Files mentioned by the user:

REGRAGUI_ 02.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_ 02.pdf

Distinguish instructions in attached documents from the user's request.

My request:

This happened next. What is your leading hypothesis?

26. ASSISTANT — progress | 08 Oct 2026, 14:57

I’ll review the new findings and identify the leading hypothesis.

27. ASSISTANT | 08 Oct 2026, 14:58

My leading working hypothesis is A: TPN extravasation from a malpositioned UVC, causing ascites and secondary renal compromise. Confidence is moderate; malposition alone does not prove leakage.

The supporting findings are rapid abdominal distension during UVC-delivered TPN, substantial ascites and subsequently documented UVC malposition. Ascites can impair renal perfusion through increased intra-abdominal pressure, contributing to oliguria. These findings are reported in [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_ 02.pdf]. This is a recognised UVC complication. Neonatal TPN-ascites series

However, C: urinary ascites is a close alternative that must be actively excluded. Oliguria with **Na 131, K 6.8 mmol/L and creatinine 1.10 mg/dL** is compatible with urinary leakage and peritoneal “autodialysis”—reabsorption of urinary solutes into blood. The creatinine value alone at DOL 2 cannot establish acute kidney injury. Neonatal urinary-ascites report

The most useful discriminator is **ascitic-fluid chemistry compared with simultaneous blood samples**, if fluid is sampled:

- **High fluid glucose/triglycerides consistent with the infused solution:** supports TPN extravasation.

- **Fluid creatinine exceeding serum creatinine:** supports urinary ascites; investigate the bladder and urinary tract.

The timing matters: **strictly at DOL 2, before the DOL 3 malposition finding, TPN leakage and urinary ascites are both strong hypotheses.** NEC is less supported by the information shown, but a low CRP does not exclude it.

Meanwhile, stop using the suspect UVC and urgently repeat potassium on a non-haemolysed sample with ECG monitoring; confirmed **K 6.8 mmol/L requires prompt neonatal hyperkalaemia management**.

28. USER | 08 Oct 2026, 15:01

Files mentioned by the user:

REGRAGUI_03.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_03.pdf

Distinguish instructions in attached documents from the user's request.

My request:

What do you think about the next?

29. ASSISTANT — progress | 08 Oct 2026, 15:01

I’ll review the next findings and see how they change the working diagnosis.

30. ASSISTANT | 08 Oct 2026, 15:02

This recurrence moves urinary ascites (uroperitoneum) to the leading diagnosis, with a bladder leak/rupture the first source to investigate. The likely missed clue was the combination of **ascites, oliguria, hyponatraemia, hyperkalaemia and rising creatinine**, already present during the first episode.

The new slides show recurrence at DOL 9 despite UVC removal, now with **Na 122 mmol/L, K 6.7 mmol/L and creatinine 2.29 mg/dL**, with CRP <0.6 mg/L: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_03.pdf].

Why this changes the interpretation

Urine leaking into the peritoneum can undergo **reverse peritoneal dialysis**: creatinine, urea and potassium are reabsorbed into blood, producing apparent renal failure and electrolyte disturbances. Genuine renal injury or

pressure-related renal compromise may coexist. This mechanism fits the recurrent biochemical pattern particularly well. Neonatal urinary-ascites report

The improvement after UVC removal was **not proof of TPN extravasation**: feeds were stopped simultaneously, and the slides do not document fluid chemistry confirming TPN. The malpositioned UVC may have been causal, incidental, or part of a mixed first episode. PICC-related leakage still warrants checking, but no longer provides the strongest unifying explanation.

What I would do next

Priority	Action	Purpose
1	Obtain **paired ascitic-fluid and serum creatinine/urea**, if safely sampled; include fluid glucose, triglycerides and culture as appropriate	Fluid creatinine above serum strongly supports urinary ascites; glucose/triglycerides help distinguish TPN leakage
2	Targeted **renal and bladder ultrasound**, including bladder filling, wall, upper-tract dilatation and possible urinoma	Identify urinary obstruction or a possible leak source; the shown liver-region images do not adequately assess this
3	Urgent paediatric urology review and **gentle bladder catheter drainage** by an experienced clinician	Decompress the urinary tract and measure urine output; avoid traumatic instrumentation
4	**Retrograde cystography/VCUG** with paediatric radiology/urology	Demonstrate bladder extravasation and assess outlet anatomy
5	Reassess ascites, urine output and serum chemistry after drainage	Rapid improvement supports uroperitoneum and clarifies the contribution of true renal dysfunction

Urinary ascites and spontaneous bladder rupture can occur despite normal antenatal urinary imaging, including in female infants. **Posterior urethral valves would not explain this female infant's presentation.** Bladder-rupture series, Female preterm urinary-ascites report

In parallel, treat the electrolyte abnormalities urgently: ECG monitoring, prompt non-haemolysed potassium confirmation and neonatal hyperkalaemia treatment; controlled sodium correction with frequent measurements. Tense ascites causing respiratory or circulatory compromise may require drainage.

My answer to "What did we miss?": likely **a urinary leak with peritoneal autodialysis**, obscured by the plausible UVC explanation. It is now the strongest hypothesis, but fluid analysis and urinary-tract imaging must confirm it.

31. USER | 08 Oct 2026, 15:02

Files mentioned by the user:

REGRAGUI_04 copy.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_04 copy.pdf

Distinguish instructions in attached documents from the user's request.

My request:

Address the last question. Give your differential diagnoses, examinations and management.

32. ASSISTANT — progress | 08 Oct 2026, 15:02

I'll read the new findings and address the last question with a ranked differential, examinations and management.

33. ASSISTANT | 08 Oct 2026, 15:03

The fluid confirms urinary ascites; the remaining question is where the urine is leaking. My priority is to identify a **bladder-dome or bladder-connected urachal leak** using targeted ultrasound and retrograde cystography.

Among the slide's choices, **C—urachus-related—is plausible and merits specific investigation**, but the evidence shown does not yet distinguish it from ordinary bladder rupture or an upper urinary-tract leak.

Ascitic creatinine is **5.0 mg/dL versus serum 2.29 mg/dL**, giving a ratio of **2.18**. Together with the low triglycerides and fluid glucose below serum glucose, this strongly supports urine rather than TPN as the fluid source: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/REGRAGUI_04 copy.pdf]. A fluid-to-serum creatinine ratio above 1 supports uroperitoneum. Female preterm urinary-ascites report

Differential diagnoses

Priority	Diagnosis	Supporting findings	What would distinguish it
1	**Bladder rupture/leak**, spontaneous, pressure-related or iatrogenic	Recurrent uroperitoneum, oliguria and electrolyte disturbances; normal prenatal ultrasound does not exclude it	Cystography showing intraperitoneal extravasation; review urinary catheterisation, bladder distension and other instrumentation
2 — closely competing	**Bladder-connected urachal anomaly with rupture/leak**, such as a ruptured vesicourachal diverticulum or patent tract	Neonatal presentation and possible bladder-dome source; specifically raised by the slide	Ultrasound along the bladder-to-umbilicus tract and cystography demonstrating communication/leak. **A patent urachus usually drains at the umbilicus; patency alone does not explain intraperitoneal urine**
3	**Upper-tract leak** from calyceal/renal pelvic rupture, usually associated with obstruction	Can produce urinary ascites; congenital urinary pathology may have escaped prenatal detection	Hydronephrosis, urinoma, ureteric abnormalities; targeted imaging if cystography is negative
4	**Underlying outlet obstruction or bladder dysfunction**, causing secondary rupture	Could explain recurrent high-pressure leakage	Bladder wall/residual volume, urethral anatomy, genital examination and neurological/spinal findings; assess for urethral anomaly or neurogenic dysfunction
Low likelihood as the explanation	Bowel perforation, NEC or TPN extravasation	May coexist, but do not explain the urinary fluid chemistry	Investigate if bowel signs, inflammatory changes or line abnormalities persist
Not applicable to the documented female anatomy	**Posterior urethral valves**	—	This male-specific lesion is not a suitable explanation here

Importantly, an **isolated noncommunicating urachal cyst** would not explain urine-rich ascites unless a urinary communication were demonstrated. Normal antenatal scans have been reported in neonatal bladder rupture. Bladder-rupture series, Urachal imaging review

Examinations, ranked by priority

Priority	Examination	Purpose and management consequence
1	**Targeted renal–bladder–urachal ultrasound**, preferably before decompression if this causes no delay	Assess kidneys/ureters, bladder wall and filling, urinoma, and the midline tract from bladder dome to umbilicus. Directs the search towards bladder/urachus or upper tract

Priority	Examination	Purpose and management consequence
2	**Retrograde cystogram/VCUG**, with neonatal technique and controlled filling by paediatric radiology/urology	Localise bladder extravasation, reveal a communicating urachal remnant and assess outlet anatomy. Obtain appropriate views/post-drainage images; avoid overdistension
3	Focused examination and history	Inspect umbilicus for urine, swelling or abnormal healing; inspect external genitalia, sacrum and neurological function. Review catheterisation and umbilical procedures without assuming the UVC caused the urinary lesion
4	Serial electrolytes, glucose, blood gas, urea/creatinine; ECG and strict fluid balance	Establish immediate severity and response to urinary diversion. Creatinine may reflect both peritoneal reabsorption and genuine kidney injury
5	Urine culture; ascitic culture if sampled; blood culture if clinically indicated	Identify infection affecting treatment and surgical timing
6 — if unresolved	Specialist-directed repeat cystography, cystoscopy or upper-tract imaging	A negative study does not fully exclude an intermittent or temporarily sealed leak. Choose further imaging from the ultrasound findings; CT is not the routine next step

Cystography can demonstrate bladder leakage, while fluid chemistry establishes urinary origin. Neonatal urinary-ascites series

Immediate management

- **Urgent neonatal, paediatric urology/surgery and nephrology involvement.**

- **Gentle bladder catheter drainage** by an experienced clinician, confirming position and maintaining free drainage. Avoid repeated traumatic attempts. Do not delay decompression in a compromised infant merely to complete imaging.

- **Drain the peritoneal fluid if tense ascites compromises ventilation, perfusion or renal function**, using ultrasound guidance and controlled drainage. Measure bladder and peritoneal outputs separately.

- Treat **K 6.7 mmol/L urgently**: continuous ECG, rapid non-haemolysed confirmation, stop potassium intake and use the neonatal hyperkalaemia pathway. Calcium gluconate is indicated for ECG changes; insulin/glucose and other potassium-shifting treatments require close monitoring. Avoid potassium-binding resins in this preterm infant because of intestinal injury risk. Neonatal hyperkalaemia guidance

- Correct **Na 122 mmol/L carefully**, accounting for duration and symptoms. In the absence of neurological symptoms, generally aim for a rise no greater than **6–8 mmol/L in 24 hours**, with frequent checks. After leak control, diuresis may cause unexpectedly rapid correction. Symptomatic hyponatraemia requires protocol-based hypertonic saline.

- Tailor fluids to perfusion, weight, electrolytes and measured losses; avoid reflex fluid boluses for oliguria when urine is leaking into the abdomen.

- Temporarily withhold feeds if distension or instability is significant; provide glucose/nutrition through verified access. Use antibiotics for suspected infection or indicated perioperative prophylaxis.

Definitive treatment and follow-up

Treatment depends on the anatomy and whether leakage stops with drainage. Selected small neonatal bladder leaks have healed with catheter drainage, but a large defect, persistent/recurrent leakage, infected urine or clinical deterioration favours repair. Intraperitoneal rupture should receive prompt surgical consideration rather than a prolonged empirical observation period. Neonatal series, EAU paediatric bladder-trauma guidance

A **symptomatic leaking urachal remnant** may require excision and closure of its bladder attachment. An upper-tract leak requires relief of the underlying obstruction, sometimes with stenting or nephrostomy.

Before removing urinary drainage, document resolution and usually confirm healing by specialist-directed cystography. Follow renal function, ultrasound, blood pressure, urine output and recurrence. Explain to the family that biochemical “renal failure” may improve rapidly after stopping peritoneal urine reabsorption, but persistent abnormalities require assessment for true renal injury.

Clinical conclusion: urinary ascites is established with high confidence; **a bladder/urachal leak is the leading anatomical hypothesis**, still unconfirmed. The decisive next investigation is **targeted urinary ultrasound followed by retrograde cystography**, alongside urinary diversion and urgent electrolyte management.

34. USER | 08 Oct 2026, 15:13

Files mentioned by the user:

PPT when twins don't match_ 01.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/PPT when twins don't match_ 01.pdf

Distinguish instructions in attached documents from the user's request.

My request:

This is the next case. Answer question 1 and motivate your rationale

35. ASSISTANT — progress | 08 Oct 2026, 15:13

I’ll read the new case and answer question 1, explaining which findings support the choice.

36. ASSISTANT | 08 Oct 2026, 15:14

My preferred answer is B: monochorionic dizygotic twins, provided monochorionicity is confirmed. This is the leading hypothesis, not yet a proven diagnosis.

The key clue is **IVF/ICSI with transfer of two embryos**, followed by an apparently MCDA pregnancy with one boy and one girl: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/PPT when twins don't match_ 01.pdf].

Why B fits

- **Chorionicity describes placentation; zygosity describes genetic origin.** Monochorionic twins are usually monozygotic, but rare monochorionic dizygotic pregnancies are documented, including after double-embryo transfer.

- Two independently fertilised embryos readily explain the discordant sex. **Early fusion of their outer trophoblastic tissues**, while the embryonic lineages remain separate, is a proposed mechanism for a shared chorion—not a mechanism demonstrated in this case.

- Placental vascular connections can exchange haematopoietic cells, producing **XX/XY blood chimerism** in both infants without implying that either has a disorder of sex development. Documented case after two-embryo transfer, Genetically confirmed monochorionic dizygotic twins

Why the other answers remain alternatives

Option	Assessment
A: actually DCDA	Must be excluded. Fused dichorionic placentas can resemble one placenta. Review early ultrasound and placental membrane histology; discordant sex alone does not establish an obstetric error.
C: postzygotic sex-chromosome loss	Possible—for example, an initially XY embryo giving rise to XY and 45,X/mosaic twins—but requires genetic evidence.

Option	Assessment
D: monozygotic twins with discordant sex development	Also possible, but no genital, endocrine or molecular findings supporting it are provided.

How I would confirm B: review first-trimester chorionicity and placental histology, then perform **autosomal STR/SNP zygosity testing on non-blood tissue from both infants**, alongside sex-chromosome studies. Blood-only testing can mislead because of chimerism; buccal samples are useful, with another tissue such as skin fibroblasts if results remain ambiguous.

Rationale: confirmed monochorionicity plus genetic differences across autosomal markers would establish monochorionic dizygotic twinning. The dual-embryo transfer makes this explanation particularly compelling here.

37. USER | 08 Oct 2026, 15:17

Files mentioned by the user:

PPT when twins don't match_02.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/PPT when twins don't match_02.pdf

Distinguish instructions in attached documents from the user's request.

My request:

Answer question 2. Motivate your rationale. What examinations would you consider? What are your differential diagnoses ?

38. ASSISTANT — progress | 08 Oct 2026, 15:17

I'll read the next slides, answer question 2, and explain which examinations would distinguish the possible diagnoses.

39. ASSISTANT | 08 Oct 2026, 15:18

The best answer to question 2 is C: blood chimerism. Both infants have XX and XY lymphocyte populations, most plausibly because blood-forming cells were exchanged through placental vascular connections. **Whether the chimerism is confined to blood remains to be established.**

The slides report confirmed dizygosity, typical male and female external genitalia, no uterus in the boy, a uterus in the girl, and the same approximately **70% XX / 30% XY pattern in cultured lymphocytes**: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/PPT when twins don't match_02.pdf].

Why this is chimerism

- **Chimerism:** cells originating from **two different zygotes** coexist in one individual.

- **Mosaicism:** genetically different cell populations arise from **one zygote**, through a postzygotic event.

In these dizygotic twins, placental anastomoses can allow reciprocal transfer and engraftment of haematopoietic progenitors, producing persistent blood chimerism. Similar cases have shown mixed XX/XY blood cells but a single sex-chromosome constitution in non-blood tissues. Documented monochorionic dizygotic twins, Case with identical blood mixtures in both infants

The percentages describe the sampled lymphocytes—not the whole infant, gonads or reproductive anatomy. Culture can also affect measured proportions. Furthermore, interphase X/Y FISH identifies sex-chromosome signals; a full "46,XX/46,XY" designation requires complementary chromosome analysis.

Examinations I would consider

Priority	Examination	Purpose
1	Review the existing zygosity test: tissue sampled, method and informative autosomal markers	Confirm that dizygosity was established independently of potentially misleading mixed blood DNA
2	**X/Y FISH and autosomal STR/SNP testing on non-blood tissue from both infants**, initially buccal epithelial cells	Determine whether each infant has a predominant individual tissue genotype or evidence of broader chimerism. Use epithelial-cell identification because buccal samples can contain leukocytes
3	Independently collected peripheral blood: uncultured FISH, chromosome analysis and informative autosomal markers	Confirm the finding, exclude sample contamination and demonstrate that the second population matches the co-twin. Review transfusion history
4	Skin fibroblasts or another suitable tissue **if buccal results are mixed or inconclusive**	Clarify genuine non-haematopoietic chimerism; biopsy is not automatically necessary
5	Formal placental pathology report, especially dividing-membrane histology; review early ultrasound	Confirm monochorionicity. A placental photograph or one placental mass alone is insufficient
6	Focused genital/gonadal examination and review of pelvic ultrasound	Document testes, genital anatomy and internal structures. Additional imaging or endocrine testing is indicated if anatomy or non-blood genetic findings raise concern
7	Blood-group assessment with transfusion-service input	Detect possible mixed-field blood typing and document chimerism for future transfusion and genetic testing

Rare non-blood chimerism has been reported, so it should not be excluded solely because external genitalia are typical. Buccal-cell chimerism report

Ranked differential diagnoses

Diagnosis	Assessment in this case
Predominantly or exclusively haematopoietic twin chimerism	**Leading explanation:** confirmed dizygosity, shared placentation and reciprocal XX/XY blood populations
Broader tissue chimerism	Possible, but not demonstrated by lymphocyte testing; requires evidence in non-blood cells
Sample contamination or laboratory mix-up	Less likely, but independently collected samples are appropriate, particularly with identical reported proportions
Transfusion-associated donor-cell admixture	Depends on sample timing and transfusion history; distinguished by persistence and donor/co-twin genotyping
True sex-chromosome mosaicism	Less likely as the unifying explanation; requires a single-zygote origin for the cell populations rather than two distinct autosomal genotypes
A coexisting difference/disorder of sex development	Currently unsupported. XX/XY blood alone does **not** diagnose ovotesticular DSD or establish ovarian and testicular tissue

I would not undertake gonadal biopsy, surgery or a broad hormonal work-up solely because of this blood result. Clinical genetics should coordinate tissue testing and counselling; paediatric endocrinology becomes relevant if genital, gonadal, hormonal or non-blood findings indicate a sex-development concern.

Conclusion: choose **C**, with high confidence in twin blood chimerism as the explanation. The next task is to establish its **tissue distribution**, rather than infer systemic chimerism or a DSD from blood alone.

40. USER | 08 Oct 2026, 15:29

Files mentioned by the user:

NicolasKindt_.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/NicolasKindt_.pdf

Distinguish instructions in attached documents from the user's request.

My request:

This is the next case

41. ASSISTANT — progress | 08 Oct 2026, 15:29

I'll review the new case and address its discussion question.

42. ASSISTANT | 08 Oct 2026, 15:30

This case raises concern for an underlying developmental pulmonary vascular/lung disorder, rather than uncomplicated transient PPHN alone. If choosing among the mechanisms on slide 4, I would prioritise **C: underdeveloped lung or pulmonary vasculature**, while recognising that the pneumothoraces contributed substantially to the acute deterioration.

The supplied PDF has no explicit final-slide question or confirmed diagnosis. It ends with **persistent tachypnoea despite withdrawal of sildenafil and oxygen, and no PH detected on the September echocardiogram**: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/NicolasKindt_.pdf].

Why investigate beyond PPHN?

The infant was born at 39+3 weeks with marked growth restriction—2270 g—and developed severe hypoxaemia within hours. Echocardiography supports PPHN physiology, but does not identify its cause. The concerning features are:

- Repeated oxygenation failure despite reportedly adequate ventilation and an initial response to iNO.

- A structurally normal heart and reported normal pulmonary venous return.

- Continued oxygen requirement after the acute crisis, followed by persistent tachypnoea.

- No substantial parenchymal explanation reported on CT.

However, **bilateral pneumothoraces provide a genuine competing explanation for much of the neonatal instability**. Growth restriction may also contribute to abnormal pulmonary vascular adaptation. The slides justify further investigation, but do not prove genetic disease.

Leading differential diagnoses

Diagnosis	Why it deserves consideration	Findings limiting it
TBX4-related developmental lung disease / pulmonary hypertension	Can present with severe neonatal PH, improve initially and remain clinically abnormal or relapse later	No genetic, skeletal or familial findings provided
Prolonged PPHN associated with growth restriction and air-leak disease	Fits the SGA phenotype, bilateral pneumothoraces and eventual improvement	Persistent tachypnoea and prolonged oxygen requirement need an explanation
Atypical alveolar capillary dysplasia with misalignment of pulmonary veins—FOXF1-related	Severe disproportionate PH; microscopic vascular disease is not excluded by normal pulmonary venous return on echo	Rapid recovery and months of improvement strongly oppose classic diffuse ACD; atypical forms remain possible
Other developmental/parenchymal lung disease, including pulmonary interstitial glycogenosis or surfactant dysfunction	May cause neonatal respiratory failure and secondary PH	Reportedly unrevealing CT and rapid extubation reduce support, without excluding all microscopic disease

Diagnosis	Why it deserves consideration	Findings limiting it
Pulmonary vein stenosis or evolving cardiac/vascular disease	Important treatable causes of persistent respiratory symptoms	Initial assessment was reassuring; requires reassessment if symptoms persist
A separate cause of current tachypnoea—aspiration, airway disease, anaemia or residual lung injury	PH may have resolved while another problem persists	Requires current clinical and physiological assessment

Developmental lung disease can present with PH even without obvious parenchymal abnormalities. Interdisciplinary consensus on developmental lung disease–associated PH

Examinations I would prioritise now

1. **Reassess the persistent tachypnoea:** respiratory rate during quiet sleep, work of breathing, feeding symptoms, growth, resting/feeding/sleep saturations and haemoglobin. Measure CO□ if ventilation is uncertain.

2. **Repeat expert echocardiography:** RV size/function, septal configuration, shunting and pulmonary vein Doppler. A single reassuring echo does not explain persistent symptoms.

3. **Review the complete CT and neonatal imaging** with paediatric radiology, including lung volumes, vascular anatomy and the contribution of air leaks.

4. **Clinical genetics assessment and a developmental lung disease/PH panel**, prioritising **TBX4 and FOXF1**, with deletion/duplication analysis and appropriate FOXF1 regulatory-region coverage. Broader genes depend on phenotype. Testing is justified by the unusual severity and course, not by tachypnoea alone.

5. **Feeding/swallow assessment** if symptoms suggest aspiration.

6. **Cardiac catheterisation or lung biopsy only if unresolved disease warrants it:** recurrent PH, significant unexplained hypoxaemia or deterioration. Neither is a routine next step in a clinically improving infant with reassuring cardiac assessment.

TBX4 testing should include copy-number analysis. FOXF1 testing is recommended for otherwise unexplained refractory neonatal PH in the appropriate lung-disease phenotype. Developmental PH consensus, ATS infant lung-disease guideline

Management at the current stage

Arrange joint paediatric respiratory and PH follow-up, monitor growth and oxygenation during sleep/feeding, and investigate the tachypnoea before attributing it to residual PH. **I would not restart sildenafil solely for tachypnoea with no demonstrated PH.** Oxygen should follow measured need.

If severe hypoxaemia recurs, reassess immediately for pneumothorax, infection, aspiration and renewed PH. Vasodilator treatment should be guided by cardiac physiology and specialist review.

My working conclusion: possible developmental pulmonary vascular disease, with **TBX4-related disease a leading genetic candidate**. Confidence in a specific diagnosis is low. The improvement is reassuring, but persistent tachypnoea warrants continued investigation and surveillance.

43. USER | 08 Oct 2026, 15:36

What examinations do you suggest

44. ASSISTANT | 08 Oct 2026, 15:36

I would prioritise reassessing pulmonary vascular physiology, documenting oxygenation during sleep and feeding, and investigating developmental/genetic lung disease. For this infant, persistent tachypnoea warrants investigation even though the latest echo did not show PH.

Priority	Examination	Purpose and effect on management
1	**Clinical respiratory and growth assessment**	Confirm tachypnoea during quiet sleep; assess retractions, feeding fatigue, auscultation, weight/length/head growth and family history. Determines urgency and whether symptoms suggest aspiration, airway disease or cardiopulmonary limitation
2	**Expert repeat echocardiography**	Assess RV pressure/function, septal shape, shunts, LV function and **all pulmonary veins with Doppler**. Recurrent PH or suspected venous obstruction changes treatment and may justify catheterisation
3	**Room-air oximetry during sleep and feeding**, preferably overnight recording	Detect occult or episodic hypoxaemia and determine whether oxygen withdrawal remains appropriate. Add CO□ monitoring if hypoventilation is suspected
4	**Genetic testing through clinical genetics**	Prioritise **TBX4 and FOXF1**, including deletion/duplication analysis and appropriate FOXF1 regulatory-region testing. A broader developmental lung disease/PH panel can include surfactant-related genes and other phenotype-directed candidates
5	**Expert review of the complete chest CT and previous radiographs**	Reassess lung volumes, subtle parenchymal abnormalities, vascular anatomy and residual air-leak injury. Avoid repeating CT before reviewing the existing study
6	**Targeted blood tests:** FBC, blood gas, electrolytes; consider BNP/NT-proBNP	Identify anaemia, impaired ventilation or metabolic drivers of tachypnoea. BNP trends can support assessment of cardiac strain but cannot exclude PH
7 — if feeding-related symptoms	Feeding/swallow assessment, followed by **VFSS or FEES** when indicated	Identify aspiration contributing to tachypnoea, desaturation or poor growth
8 — if clinically suggested	ENT/airway assessment, bronchoscopy or polysomnography	Investigate stridor, suspected malacia, recurrent atelectasis, apnoea or abnormal overnight monitoring
9 — specialist escalation	**Cardiac catheterisation**	If PH recurs, non-invasive findings conflict, or significant unexplained hypoxaemia persists: measure haemodynamics and evaluate vascular disease before major treatment escalation
10 — selected cases only	**Surgical lung biopsy with expert pathology**	Consider if significant unexplained disease persists despite imaging/genetics and histology would change management—for example, suspected ACD or pulmonary interstitial glycogenosis. Not a routine next step in a stable, improving infant

Genetic testing is particularly relevant after severe, disproportionate neonatal PH. **A normal CT does not exclude microscopic developmental vascular disease, and a negative genetic panel does not exclude every form of it.** Current consensus supports integrated genetic, imaging and haemodynamic assessment. Developmental lung disease–associated PH consensus

My first three actions would be: expert echo review, overnight/feeding oxygenation assessment, and genetics referral with **TBX4/FOXF1-focused testing**. I would reserve catheterisation and biopsy for persistent objective abnormalities or deterioration.

45. USER | 08 Oct 2026, 15:37

What would you find in the genetic testing if TBX4 testing was positive?

46. ASSISTANT — progress | 08 Oct 2026, 15:37

I'll check what a positive TBX4 result would look like and how it would be interpreted in this infant.

47. ASSISTANT | 08 Oct 2026, 15:37

A diagnostic positive result would usually identify a heterozygous pathogenic or likely pathogenic alteration affecting TBX4—one of the infant's two copies. It could take either form:

Genetic finding	Typical report
Sequence variant	A nonsense, frameshift, splice-site or disease-causing missense variant, described with its DNA/protein change and classification
Deletion	Loss of one or more TBX4 exons, the whole gene, or a larger **17q23.1–q23.2 deletion encompassing TBX4**; the report specifies its extent and other genes involved

Many variants impair TBX4 function; some disease-associated missense variants have different functional effects. Therefore, **finding any TBX4 variant is not automatically diagnostic**: a *variant of uncertain significance* would not confirm the cause. TBX4 genotype–phenotype study

In this infant, a convincing pathogenic result would support TBX4-related developmental lung disease/pulmonary hypertension. It could explain severe neonatal PH followed by improvement, with a continuing risk of PH later in infancy or childhood. It would not predict severity or prove that current tachypnoea represents active PH. Neonatal and paediatric TBX4 cohort

I would then:

- **Test both parents** to establish whether the alteration is de novo or inherited. TBX4 disease is generally autosomal dominant, with variable expression and reduced penetrance.

- Examine for **small-patella syndrome features**, including patellar, pelvic and foot abnormalities; their absence does not exclude TBX4-related lung disease.

- Continue pulmonary hypertension surveillance and offer genetics-led assessment of relatives.

The actual variant cannot be inferred from the slides. A positive report needs its exact alteration, classification and inheritance to interpret it properly.

48. USER | 08 Oct 2026, 15:38

What do you suggest for follow-up management? What would you tell the parents?

49. ASSISTANT — progress | 08 Oct 2026, 15:38

I'll frame follow-up and counselling for a confirmed pathogenic TBX4 result, while distinguishing the child's current recovery from the longer-term risk.

50. ASSISTANT | 08 Oct 2026, 15:39

Assuming a pathogenic/likely pathogenic TBX4 result is confirmed, I would continue long-term follow-up through a paediatric pulmonary hypertension service and respiratory team—even after oxygen and sildenafil have been stopped. Recovery is reassuring, but TBX4-associated PH can recur after an apparently normal interval. TBX4 neonatal/paediatric cohort

Follow-up for this infant

Area	Suggested plan
Cardiopulmonary surveillance	Review now because tachypnoea persists. A reasonable individualised schedule is **every 1–3 months initially**, extending to 3–6 months when stable. Retain at least annual long-term assessment; this schedule is a clinical proposal, not a validated TBX4-specific protocol
At each visit	Respiratory rate/effort, feeding tolerance, growth, resting saturation, examination and expert echocardiography according to clinical course. ECG and BNP/NT-proBNP trends can provide additional information
Sleep and feeding oxygenation	Overnight oximetry and assessment during feeds; add CO□ monitoring if indicated. Confirm that remaining off oxygen is appropriate
Persistent tachypnoea	Investigate anaemia, aspiration, airway disease and residual/developmental lung disease rather than assuming recurrent PH
Medication	**Do not restart sildenafil solely because TBX4 is positive.** Treat demonstrated PH through the specialist team; provide oxygen for documented hypoxaemia
Escalation	Earlier review for deterioration. Consider catheterisation if PH recurs or symptoms and non-invasive findings conflict. Avoid routine repeat CT or lung biopsy in a stable child
Associated features	Assess knees/patellae, pelvis, feet and gait as development progresses; involve orthopaedics/physiotherapy when needed. Monitor development, particularly if a larger deletion affects additional genes
Prevention and planning	Routine vaccinations and seasonal RSV prevention according to local eligibility; smoke-free environment, good nutrition, and a documented respiratory emergency plan. Discuss travel and anaesthesia with the treating team if respiratory abnormalities remain

Long-term surveillance is supported by genetic PH guidance, although the ideal TBX4-specific screening interval remains uncertain. Genetic counselling and screening consensus

Genetics and family follow-up

Test both biological parents for the infant's alteration. If inherited, offer genetics-led testing and cardiopulmonary assessment to relevant relatives, including apparently healthy carriers.

A carrier has a **50% chance of transmitting the alteration in each pregnancy**, but transmission does not predict disease severity. If it is de novo, recurrence in another pregnancy is usually low, though not zero because parental germline mosaicism is possible. Reproductive counselling should follow the exact result.

What I would tell the parents

[Reusable writing block]

“Your baby’s improvement is encouraging. At present, the scans do not show pulmonary hypertension, and being able to stop oxygen and medication is a positive sign.

TBX4 helps the lungs and their blood vessels develop. This genetic finding may explain why your baby had such severe breathing and circulation problems after birth. It was not caused by anything you did.

Some children remain well; others develop lung problems or pulmonary hypertension again later. The genetic result cannot tell us exactly what will happen for your child. We will therefore continue checking breathing, growth and heart function, so that any change is recognised early.

Please contact us promptly if breathing becomes faster or harder than usual, feeding becomes tiring, or weight gain slows. Blue colour, collapse, marked breathlessness or unusual reduced responsiveness need emergency assessment.

We will also offer genetic counselling and testing for you, because a parent can carry this alteration without obvious symptoms. Our aim is to support your child’s normal activities and development while keeping an appropriate watch on their lungs and circulation.”

The key balance is continued surveillance without treating the genotype alone or predicting a poor outcome from it.

51. USER | 08 Oct 2026, 15:45

Files mentioned by the user:

Tanguy _ 01.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/Tanguy _ 01.pdf

sound.wav: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/sound.wav

Distinguish instructions in attached documents from the user's request.

My request:

This is the next case

52. ASSISTANT — progress | 08 Oct 2026, 15:46

I’ll review the case slides and check the accompanying audio for any relevant clinical information.

53. ASSISTANT | 08 Oct 2026, 15:46

My main concern is acquired upper-airway obstruction—particularly a subglottic cyst or post-intubation stenosis—unmasked or worsened by rhinovirus. I would request urgent ENT airway assessment rather than attribute progressive stridor and desaturations to the viral result alone.

The infant was born at **26+2 weeks**, had two early intubations, and developed new stridor with increased work of breathing and progressive desaturation on **day 58, at 34+4 weeks PMA**. The final slide contains an audio icon but no written question: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/Tanguy _ 01.pdf]. I could access the WAV file, but cannot reliably listen to or classify it with the available tools; I therefore cannot establish whether the sound is inspiratory or biphasic.

Leading differential diagnoses

Diagnosis	Rationale
Acquired subglottic cyst	Prematurity and previous intubation are characteristic risk factors. Presentation may be delayed for weeks or months after apparently successful extubation

Diagnosis	Rationale
Post-intubation subglottic stenosis or granulation tissue	A narrowed airway may become symptomatic when a viral infection adds mucosal swelling
Viral laryngotracheal inflammation/oedema	Rhinovirus could contribute, but does not exclude an underlying structural lesion
Vocal-fold immobility or posterior glottic injury	Consider especially with a weak/abnormal cry, aspiration or biphasic stridor
Laryngomalacia/tracheomalacia	Infection may reveal dynamic obstruction; the late onset makes previously silent congenital disease less compelling
Subglottic haemangioma or another airway lesion	Less likely, but progressive stridor at this age warrants exclusion

Subglottic cysts are a recognised complication even after neonatal intubation and should be considered in previously intubated preterm infants presenting with stridor. Preterm-infant series, Infancy series

Examinations

1. **Immediate severity assessment:** continuous heart rate/SpO□, respiratory effort, air entry, apnoea and blood gas/CO□ if deterioration continues. Document the respiratory phase of the noise and cry quality.

2. **Urgent flexible nasolaryngoscopy**, if sufficiently stable, to assess supraglottic anatomy and vocal-fold movement.

3. **Direct microlaryngoscopy and bronchoscopy** if obstruction is significant or the flexible examination is unrevealing. This is essential to inspect the subglottis: **a normal flexible laryngeal examination does not exclude a subglottic cyst or stenosis**.

4. Chest radiography and infection investigations as clinically indicated, without delaying airway evaluation.

Management at this stage

- Involve senior neonatology, ENT and paediatric anaesthesia early; minimise agitation and prepare a difficult-airway plan.

- Continue oxygen/respiratory support while assessing effectiveness. **Increasing HFNC alone may not overcome fixed obstruction.**

- Withhold oral feeds during significant respiratory distress and maintain glucose/hydration.

- A short dexamethasone trial may reduce inflammatory oedema, but improvement would not exclude a structural lesion and failure should prompt escalation.

- Recurrent severe desaturation, exhaustion, rising CO□ or poor air movement requires securing the airway by an experienced team; avoid repeated traumatic intubation attempts.

- If a cyst is confirmed, endoscopic marsupialisation/excision is usually considered, with surveillance for recurrence. Stenosis treatment depends on its severity and character.

The key next step is visualising the airway, including the subglottis. A subglottic cyst is a strong case-specific possibility, but the diagnosis cannot be made from the history or sound alone.

54. USER | 08 Oct 2026, 15:49

Files mentioned by the user:

Tanguy _ 02.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/Tanguy _ 02.pdf

Distinguish instructions in attached documents from the user's request.

My request:

55. ASSISTANT — progress | 08 Oct 2026, 15:49

I'll review the next slides and update the interpretation and management based on the new findings.

56. ASSISTANT | 08 Oct 2026, 15:49

The new findings strengthen concern for a glottic/subglottic obstruction. The negative MRI does not reliably exclude it. I would arrange **direct microlaryngoscopy and bronchoscopy with ENT and paediatric anaesthesia before an unplanned extubation trial**.

The slides now document **biphasic stridor**, escalation to CPAP, inflammatory mucosa/reactive oedema on bedside flexible laryngoscopy, and subsequent intubation. MRI showed no lesion, but was limited by movement artefacts and an ETT potentially compressing a lesion: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/Tanguy _ 02.pdf].

Interpretation and differential

Diagnosis	Assessment at this stage
Acquired subglottic cyst	Remains a leading possibility: prematurity, previous intubation and delayed biphasic stridor fit. Short intubation exposure does not exclude it
Post-intubation subglottic stenosis/granulation	Equally important to exclude; viral swelling may have made an existing narrowing clinically significant
Inflammatory laryngotracheal oedema	Demonstrated and likely contributes, but may coexist with a structural lesion
Glottic injury or vocal-fold immobility	Requires documented vocal-fold mobility and inspection of the posterior glottis
Subglottic haemangioma or another lesion	Less likely, but progressive biphasic stridor warrants inspection
Isolated laryngomalacia	Less convincing because the noise is biphasic and the course is progressively obstructive

Biphasic stridor suggests glottic/subglottic disease, although it does not identify the exact lesion. Bedside flexible laryngoscopy may not adequately inspect the subglottis and trachea. Neonatal stridor review

What I would do next

- Review the flexible examination and complete imaging with ENT/radiology, including whether the subglottis was actually visualised.

- Undertake **controlled operative airway endoscopy**, inspecting the glottis, subglottis and trachea. The team can manage the ETT during examination safely and treat a cyst or selected granulation lesion if found.

- Maintain effective ventilation meanwhile, minimise further airway trauma and use a short, protocol-based steroid course if indicated for oedema.

- Plan extubation jointly with ENT/anaesthesia, with appropriate rescue equipment and postoperative monitoring.

Direct/rigid laryngobronchoscopy is appropriate for identifying subglottic cysts and stenosis in symptomatic preterm infants. ATS guideline

The important distinction is that intubation has stabilised the airway; it has not established the cause. Improvement while intubated—or after steroids—would not exclude a compressed cyst or residual fixed narrowing.

57. USER | 08 Oct 2026, 15:50

Files mentioned by the user:

Tanguy _03.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/Tanguy _03.pdf

Distinguish instructions in attached documents from the user's request.

My request:

58. ASSISTANT — progress | 08 Oct 2026, 15:50

I'll review this next part and update the diagnosis and recommended next steps.

59. ASSISTANT | 08 Oct 2026, 15:51

Choose "Direct airway examination via endoscopy." Progressive **biphasic stridor requiring intubation** warrants definitive inspection of the glottis, subglottis and trachea. Neither the bedside finding of oedema nor the technically limited MRI adequately excludes an obstructing lesion.

The new slides show this question followed by direct/videolaryngoscopic and ultrasound images, but **no written diagnosis or operative report**: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/Tanguy _03.pdf].

Why this option is preferable

Option	Assessment
Direct airway endoscopy	**Best next step:** identifies the site, nature and severity of obstruction and may permit treatment during the same procedure
Repeat imaging with better sedation	May subsequently help define a lesion's extent, but does not replace direct examination; the ETT may still obscure or compress it
Intensify steroids	May reduce associated oedema, but will not reliably treat a cyst, fixed stenosis or another mass
Empirical beta-blocker trial	Appropriate only when an infantile haemangioma diagnosis is sufficiently established, with specialist monitoring
Wait for rhinovirus to resolve	Insufficient given progressive obstruction and the need for intubation

Airway endoscopy is recommended for unexplained significant respiratory symptoms in previously premature infants; direct/rigid examination identifies glottic and subglottic pathology. ATS guideline

What I make of the new images

The endoscopic stills suggest **a focal tissue prominence narrowing the airway**, but I cannot reliably classify it as a cyst, haemangioma, granulation tissue or oedematous mucosa from these images alone. The ultrasound needs its formal interpretation and Doppler findings. I would therefore avoid calling this a confirmed subglottic cyst.

My leading differential remains:

- **Acquired subglottic cyst**, given prematurity, previous intubation and delayed presentation.

- **Subglottic stenosis/granulation with superimposed inflammation.**

- **Subglottic haemangioma**, particularly if the lesion is vascular on endoscopy/Doppler.

Management should follow the endoscopic diagnosis: marsupialisation for an obstructing cyst; severity-directed treatment for stenosis; or specialist-led propranolol for a confirmed haemangioma. In this very premature infant, propranolol initiation requires particular caution and monitoring for hypoglycaemia, bradycardia, hypotension and bronchospasm. Subglottic cyst series, AAP haemangioma guideline

The immediate priority is a controlled ENT/anaesthetic airway examination and a planned extubation strategy—not further empirical treatment without establishing the obstruction's cause.

60. USER | 08 Oct 2026, 15:56

The diagnosis was indeed a subglottic cyst. How would you manage this?

61. ASSISTANT | 08 Oct 2026, 15:56

For this infant, whose subglottic cyst has caused progressive stridor and required intubation, I would recommend endoscopic marsupialisation by paediatric ENT. Observation alone is inappropriate for this degree of obstruction.

Immediate and definitive treatment

- Maintain the secured airway and adequate ventilation while arranging treatment with **paediatric ENT, neonatal intensive care and experienced paediatric anaesthesia**. Minimise ETT movement and repeated instrumentation.

- Perform **microlaryngoscopy and bronchoscopy** to establish the cyst's extent, look for additional cysts and assess associated subglottic stenosis or granulation.

- **Widely open/deroof the cyst endoscopically**, preserving surrounding mucosa. The technique depends on anatomy and surgical expertise. Simple aspiration or rupture may provide temporary relief but is less durable than marsupialisation. Infant subglottic-cyst series

- Reserve open airway reconstruction or tracheostomy for persistent obstruction, significant associated stenosis or failure of endoscopic treatment. Associated stenosis is important to identify, but does not automatically require reconstruction. Preterm-infant series

After the procedure

- Plan extubation jointly, based on residual narrowing, postoperative oedema and respiratory stability. If continued intubation is necessary, use an appropriately sized tube and minimise trauma.

- Monitor in NICU for stridor, retractions, desaturation, apnoea and impaired ventilation. Provide respiratory support as needed.

- Give appropriate analgesia. A **short perioperative steroid course** may be considered for oedema; steroids do not treat the cyst itself. Antibiotics are guided by infection or local operative indications.

- Resume feeds once breathing is stable; obtain feeding/swallow assessment if choking, desaturation or aspiration concerns persist.

Follow-up

Arrange ENT surveillance, with repeat endoscopy timed according to operative findings and symptoms. **Recurrence is possible**, particularly with deep or multiple cysts; recurrent stridor should prompt reassessment rather than repeated empirical steroids. Persistent symptoms may also reflect residual stenosis. Recurrence series

Tell the parents that this is a benign cyst, often associated with earlier intubation in premature infants, and that endoscopic treatment usually relieves the obstruction. Teach them to seek urgent help for increasing noisy breathing with effort, blue colour, pauses in breathing or feeding difficulty. Document the airway history for future anaesthetics.

For this baby: endoscopic marsupialisation, assessment for coexisting stenosis, monitored extubation and follow-up for recurrence.

62. USER | 08 Oct 2026, 16:04

Files mentioned by the user:

The quest for the Missing Diagnosis _01- for IA copy.pdf:
/Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _01- for IA copy.pdf

Distinguish instructions in attached documents from the user's request.

My request:

This is the next case.

63. ASSISTANT — progress | 08 Oct 2026, 16:04

I'll review the new case and address the discussion question at the end.

64. ASSISTANT | 08 Oct 2026, 16:05

Yes—the reported need for phototherapy from day 2 to day 10 would concern me enough to investigate. Jaundice beginning on day 2 is common, but an eight-day treatment course in a term infant is unusual and should not automatically be labelled physiological or breast-milk jaundice.

The case currently describes a **14-day-old term infant**, appropriate birthweight, vacuum-assisted delivery, and neonatal jaundice treated from D2–D10. No bilirubin values, feeding history or examination findings are provided: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _01- for IA copy.pdf].

What I would investigate

Priority	Examination	Rationale
1	Retrieve the **bilirubin trajectory**, including peak, direct fraction, response to treatment and rebound	Establish whether phototherapy was continuously indicated, whether bilirubin rose unusually rapidly, and whether treatment was effective
2	**Current serum total and direct/conjugated bilirubin**	Distinguish unconjugated hyperbilirubinaemia from cholestasis. Given this atypical course, I would fractionate bilirubin now
3	Feeding assessment, birth-to-current weight change, hydration and urine/stool output	Identify inadequate intake, dehydration and increased enterohepatic circulation
4	Examine scalp and skin, pallor, liver/spleen and neurological status; inspect stool colour and ask about dark urine	Vacuum delivery raises the possibility of bruising or cephalohaematoma. Pale stools/dark urine suggest cholestasis; abnormal tone, poor suck or lethargy require urgent assessment
5	**FBC, reticulocytes and blood film; maternal/infant blood groups and DAT**	Assess immune haemolysis, anaemia and clues to red-cell membrane disease. A negative DAT does not exclude nonimmune haemolysis
6	**G6PD activity**, particularly if the cause is unexplained, response was poor or bilirubin rebounded	Important treatable risk factor for severe jaundice. Testing during haemolysis may be falsely reassuring and may require repetition
7	Review newborn screening; **TSH/free T4** if clinically indicated or jaundice remains unexplained	Exclude hypothyroidism; confirm screening was completed and results reviewed
8 — conditional	Urine culture/sepsis assessment if infection is suspected; liver tests, GGT, coagulation and abdominal ultrasound if direct bilirubin is elevated	Investigate according to the bilirubin fraction and clinical findings rather than ordering every test routinely

These priorities are consistent with evaluation of significant or atypical neonatal hyperbilirubinaemia. AAP guideline, NICE recommendations

My provisional differential

1. **Increased bilirubin load from bruising/cephalohaematoma**, given vacuum delivery.

2. **Haemolysis:** ABO/Rh-related disease, G6PD deficiency or hereditary spherocytosis.

3. **Suboptimal intake jaundice**, potentially followed by breast-milk jaundice.

4. **Hypothyroidism or infection**, depending on the clinical findings.

5. **Impaired bilirubin conjugation**, including UGT1A1-related disease, if substantial unconjugated jaundice persists without another explanation.

6. **Cholestatic disease**, including biliary atresia, if the direct fraction is elevated—less inferable from the current information, but essential not to miss.

The decisive first distinction is unconjugated versus conjugated jaundice. I would also verify that the prolonged phototherapy reflected persistent bilirubin above the appropriate treatment threshold. Without those values, neither severity nor a leading diagnosis can be established.

65. USER | 08 Oct 2026, 16:06

Files mentioned by the user:

The quest for the Missing Diagnosis_02.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis_02.pdf

Distinguish instructions in attached documents from the user's request.

My request:

66. ASSISTANT — progress | 08 Oct 2026, 16:06

I'll review the next findings and address the question at this stage of the case.

67. ASSISTANT | 08 Oct 2026, 16:07

I would admit this 14-day-old infant for monitored assessment. Reported recurrent apnoea, previously documented SpO□ of 88–90%, and unexplained jaundice requiring prolonged phototherapy warrant investigation even if examination and saturation are normal on arrival. This is **not a lower-risk BRUE presentation**. AAP BRUE criteria

The new slides document normal examination/echocardiography, subsequent normal saturation and discharge on D11, followed by parental reports of apnoea on D14: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis_02.pdf].

Immediate assessment and examinations

Priority	Action/examination	Rationale
1	Assess airway, breathing, circulation, temperature and **bedside glucose**; continuous ECG/SpO□ monitoring	Detect recurrent events and stabilise promptly. Give assisted ventilation for ineffective breathing
2	Detailed event history and observation during sleep/feeding	Clarify duration, respiratory effort, colour/tone changes, choking, responsiveness and intervention required; distinguish true apnoea from periodic breathing or obstruction

Priority	Action/examination	Rationale
3	Validate pulse oximetry with good waveform and another probe/site; compare pre/postductal measurements	Exclude artefact and establish whether desaturation persists
4	**Blood gas with co-oximetry**; arterial PaO□ if unexplained low saturation persists	Compare pulse oximetry with directly measured oxygenation and quantify metHb/COHb. A calculated blood-gas saturation alone is insufficient
5	FBC, reticulocytes, blood film, total/direct bilirubin; electrolytes including calcium	Reassess anaemia/haemolysis, current jaundice and metabolic causes of apnoea
6	Infection evaluation guided by condition and history	Neonatal infection may present with apnoea. If unwell or events are confirmed and unexplained, obtain cultures and consider lumbar puncture when stable; start empirical treatment promptly when indicated
7	ECG; chest radiograph, repeat cardiac assessment, EEG or feeding/airway studies according to findings	Investigate arrhythmia, respiratory disease, seizures or aspiration without an indiscriminate test battery

There is also a major inconsistency in the “normal” initial work-up

The reported electrophoresis—**HbA 95%, HbA□ 2.5%, HbF 2.5%—is an adult-like pattern, not an expected neonatal pattern.** HbF should still be a major fraction at this age. I would contact the laboratory to verify:

- Whether these are actual patient results or adult reference values.

- Sample identity, collection date and any transfusion history.

- The original chromatogram and age-specific interpretation.

Then repeat haemoglobin analysis on a correctly identified sample. Neonatal haemoglobin patterns

Differential diagnoses

- **Infection**, including sepsis/meningitis or a respiratory infection.

- **Feeding-related aspiration or airway obstruction.**

- **Metabolic disturbance**, particularly hypoglycaemia or hypocalcaemia.

- **Seizures or arrhythmia**, depending on event characteristics.

- **Anaemia/haemolysis with a haemoglobin abnormality.** An unstable or altered-affinity haemoglobin could potentially connect jaundice and unexpected saturation readings.

- **Methaemoglobinaemia**, inherited or acquired, particularly if low SpO□ contrasts with preserved arterial PaO□.

- Cardiopulmonary disease, less supported by the reported normal echo but not excluded by one assessment.

A rare fetal-haemoglobin variant deserves consideration if a saturation discrepancy is demonstrated: standard electrophoresis can occasionally miss such variants. It is **a hypothesis, not yet the leading confirmed diagnosis**. Neonatal cyanosis with Hb F-Cincinnati

My next steps are monitored admission, objective characterisation of the events, and blood gas/co-oximetry alongside renewed haemolysis assessment. The haemoglobin report must be verified before accepting the earlier work-up as reassuring.

68. USER | 08 Oct 2026, 16:07

Files mentioned by the user:

The quest for the Missing Diagnosis_03.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis_03.pdf

Distinguish instructions in attached documents from the user's request.

My request:

69. ASSISTANT — progress | 08 Oct 2026, 16:08

I'll review the new findings and update the interpretation and next steps.

70. ASSISTANT | 08 Oct 2026, 16:08

The key distinction is whether SpO□ 88–90% represents true hypoxaemia or a haemoglobin-related saturation abnormality. At the same time, reported apnoea and new axial hypotonia require urgent exclusion of infection, metabolic disturbance and neurological disease.

The final slide shows a 14-day-old infant with **SpO□ 88–90% in room air**, no visible cyanosis, mild axial hypotonia, residual jaundice and a soft systolic murmur. Heart rate, respiratory rate, temperature and blood pressure are otherwise reassuring: [Source file: /Users/chloedesmedt/.Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis_03.pdf].

My differential diagnosis

Diagnosis	Supporting findings	Limitations / distinguishing examinations
Haemoglobin variant or dyshemoglobinaemia—including unstable fetal Hb, low-affinity Hb or methaemoglobinaemia	Low saturation with relatively little respiratory disturbance; unexplained jaundice could indicate haemolysis	Does not automatically explain true apnoea. Obtain **arterial PaO□ and co-oximetry**, reassess haemolysis and repeat specialist Hb analysis; consider globin sequencing
Late-onset neonatal infection—sepsis, meningitis, UTI or respiratory infection	Apnoea and hypotonia can be presenting signs, even without fever	Current vital signs do not exclude infection. Cultures, inflammatory markers and lumbar puncture when indicated and safe
Cardiac shunting or pulmonary hypertension	Persistent low saturation and murmur	Previous normal echo reduces likelihood but warrants expert review if hypoxaemia is confirmed; compare pre/postductal saturation and repeat echo
Pulmonary disease or aspiration	Can cause hypoxaemia and apnoeic events	No tachypnoea or distress documented. Chest radiograph, feeding history and observed feeds; swallow assessment if indicated
Upper-airway obstruction	Could produce episodic apnoea/desaturation, particularly during sleep or feeding	Assess respiratory effort during events, airway anatomy and positional changes; ENT assessment if suggested
Metabolic/endocrine disturbance—hypoglycaemia, hypocalcaemia, electrolyte disorder; hypothyroidism or an inborn error	Hypotonia and apnoea; hypothyroidism can also cause persistent jaundice	Immediate glucose, gas, electrolytes/Ca/Mg; review screening and thyroid results. Ammonia/lactate if otherwise unexplained or deteriorating
Neurological disease—seizures, intracranial injury or impaired central respiratory control	Apnoea with hypotonia; vacuum delivery adds a reason to consider birth injury if other signs emerge	Neurological examination, video-EEG during suspicious events and targeted neuroimaging
Measurement artefact	Earlier saturation apparently normalised	Verify probe, waveform and another device/site, but do not use this explanation to dismiss the clinical history

Apnoea and reduced tone are recognised neonatal infection signs. Neonatal infection guideline

The haemoglobin findings deserve particular scrutiny. The previously reported HbA 95% / HbF 2.5% pattern is not age-appropriate unless explained, for example, by transfusion or a reporting/sample issue. A “normal” electrophoresis also does not exclude every unstable fetal-Hb variant. Neonatal Hb patterns, Hb F-Cincinnati case

My immediate discriminating tests would be:

- Validate SpO□ and obtain **blood gas with co-oximetry**, including arterial PaO□ if low saturation persists.

- Check **glucose, FBC/reticulocytes, bilirubin fractions and electrolytes**.

- Observe and document events under continuous cardiorespiratory monitoring.

- Investigate infection and repeat cardiac/respiratory assessment according to findings.

I would keep the infant admitted. A haemoglobin disorder is an important unifying hypothesis for jaundice plus low SpO□, but no specific diagnosis is established—and it must not distract from the urgent assessment of apnoea and hypotonia.

71. USER | 08 Oct 2026, 16:10

Files mentioned by the user:

The quest for the Missing Diagnosis _4.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _4.pdf

Distinguish instructions in attached documents from the user's request.

My request:

72. ASSISTANT — progress | 08 Oct 2026, 16:10

I’ll review the next findings and address the question at the end.

73. ASSISTANT | 08 Oct 2026, 16:11

I would start supplemental oxygen under monitoring, while immediately determining whether the SpO□ of 88% reflects true hypoxaemia or a haemoglobin-related measurement abnormality. I would not start empirical methylene blue.

The new slides report reassuring cardiac, pulmonary, infectious and basic metabolic investigations, no recurrent apnoea in the ED, but persistent low saturation. They do **not** provide arterial PaO□ or co-oximetry results: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _4.pdf].

My immediate approach

1. **Continue monitored admission:** ECG, reliable pulse-oximetry waveform, respiratory observation and assessment of perfusion, feeding and neurological status.

2. **Give titrated oxygen initially**, documenting the response. Avoid escalating indefinitely to achieve a normal pulse-oximeter number without understanding the discrepancy.

3. Obtain **an arterial blood gas with PaO□ and direct co-oximetry**, including oxyhaemoglobin fraction, methaemoglobin and carboxyhaemoglobin. A calculated blood-gas saturation is insufficient.

4. Recheck **haemoglobin, reticulocytes, bilirubin and lactate**, and involve paediatric haematology.

Treatment then depends on the result

Finding	Interpretation and treatment
Low PaO□	True hypoxaemia: continue oxygen and reassess pulmonary disease, shunting or hypoventilation despite the earlier reassuring studies
Preserved PaO□ with elevated metHb	Methaemoglobinaemia: remove potential oxidant exposures; treatment depends on metHb level, symptoms, anaemia and cause. Significant symptomatic disease may require methylene blue under specialist guidance
Preserved PaO□ with unexplained low SpO□ and no significant metHb	Consider an altered-affinity or optically interfering Hb variant. Seek specialist haemoglobin studies/genetics; oxygen may not normalise SpO□ and may be unnecessary once adequate oxygen delivery is established
Significant haemolytic anaemia	Treat the anaemia according to severity; red-cell transfusion may be needed. Jaundice treatment follows the measured bilirubin and age-specific threshold

Why not empirical methylene blue? SpO□ around 85–90% can occur with methaemoglobinaemia, but does not establish it or quantify severity. Methylene blue may cause haemolysis in G6PD deficiency and is generally ineffective for Hb M-related disease. Treatment should follow direct measurement and specialist interpretation. EHA/EuroBloodNet recommendations

My leading diagnostic direction remains a haemoglobin abnormality, given jaundice plus low saturation without an evident cardiopulmonary explanation. However, the decisive next step is **PaO□–co-oximetry comparison**, rather than prescribing an antidote or accepting 88% as benign. The earlier adult-like electrophoresis report still needs verification.

74. USER | 08 Oct 2026, 16:12

Files mentioned by the user:

The quest for the Missing Diagnosis _5.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _5.pdf

Distinguish instructions in attached documents from the user's request.

My request:

75. ASSISTANT — progress | 08 Oct 2026, 16:12

I'll review the new results and use them to refine the diagnosis and treatment.

76. ASSISTANT | 08 Oct 2026, 16:13

This PDF is identical to the previous version—all 13 pages—so it provides no new results. It still ends with: "Persistent saturation of 88%—what treatment would you start?" [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _5.pdf].

My answer remains **monitored supplemental oxygen initially, followed immediately by arterial PaO□ and co-oximetry** to establish whether this is true hypoxaemia, methaemoglobinaemia or a haemoglobin-related saturation discrepancy.

I would **not start methylene blue from SpO□ alone**, or keep escalating oxygen solely to normalise the displayed saturation. Treatment must follow the measured oxygenation, metHb level and clinical condition.

Please attach the next version if you intended to share additional findings.

77. USER | 08 Oct 2026, 16:13

Files mentioned by the user:

The quest for the Missing Diagnosis _6.pdf: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _6.pdf

Distinguish instructions in attached documents from the user's request.

My request:

78. ASSISTANT — progress | 08 Oct 2026, 16:13

I'll review this version for the new findings and the next clinical question.

79. ASSISTANT | 08 Oct 2026, 16:14

The father–infant similarity now strongly favours an inherited haemoglobin disorder, particularly an unstable haemoglobin variant with altered oxygen affinity and/or oxidation. It is a much stronger unifying explanation than primary lung disease.

The father has chronic haemolytic anaemia, gallstones and usual SpO□ of 85–88%; the infant has neonatal jaundice, anaemia and similarly low SpO□ despite oxygen/CPAP. Both have elevated measured methaemoglobin: [Source file: /Users/chloedesmedt/Library/CloudStorage/OneDrive-KULeuven/PhD/Congressen & Research stays/Congressen en Research Stays_2026/BVN-GBN/Cases 2026/PDF-files/The quest for the Missing Diagnosis _6.pdf].

How I interpret the blood gas

Finding	Interpretation
Venous pO□ 30 mmHg	Not evidence of arterial hypoxaemia. A venous sample cannot establish pulmonary oxygenation
pH 7.38, pCO□ 40, bicarbonate 23	No significant acid–base disturbance or hypercapnia in this sample
Hb 11.5 g/dL at two weeks	Low for age; confirm on FBC and investigate haemolysis
MetHb 4.2% in the baby; 6.8% in the father	Abnormal, but does not by itself adequately explain the entire phenotype or establish a need for antidotal treatment
Measured saturation 65.2% versus calculated 86%	A discrepancy requiring laboratory review. Calculated saturation assumes an oxygen-dissociation model that may be inappropriate for abnormal Hb

There is also a **labelling inconsistency**: slide 18 calls 65.2% *measured*, whereas slide 19 calls it *calculated*. The measured functional saturation is internally consistent with the fractions: **62.1 ÷ (62.1 + 33.2) ≈ 65.2%**. I would retrieve the original analyser reports rather than interpret the slide labels literally.

Leading differential

1. **An inherited unstable globin variant**, potentially combining haemolysis, low oxygen affinity and abnormal optical behaviour.

2. **Hb M or another oxidation-prone haemoglobin variant**, causing hereditary methaemoglobinaemia; some variants also cause haemolysis.

3. **CYB5R3-related methaemoglobinaemia**, less compelling because it does not usually explain chronic haemolytic anaemia and gallstones.

4. Separate hereditary haemolysis plus an unrelated saturation abnormality—possible, but less parsimonious.

The affected father makes an isolated fetal γ-globin variant less likely as the shared explanation. An α- or β-globin disorder becomes more relevant. Specific variants such as Hb Cheverly illustrate this phenotype, but cannot be

diagnosed from these results. Hb Cheverly study

What I would investigate next

- **Father's original haematology records**, including any molecular diagnosis.

- **Arterial PaO□ with simultaneous SpO□ and co-oximetry**, documenting FiO□.

- Haemolysis assessment: FBC, reticulocytes, smear, bilirubin, LDH and **supravital staining for Heinz bodies**.

- Specialist haemoglobin analysis, **stability testing and oxygen-affinity/P50 assessment**.

- **Globin-gene sequencing in father and infant**, prioritising HBA1/HBA2 and HBB, then phenotype-directed testing.

- If no globin explanation emerges, cytochrome-b5 reductase activity and **CYB5R3** testing.

Abnormal Hb can interfere with both pulse oximetry and co-oximetry, so even direct optical measurements require expert interpretation. Laboratory assessment of oxygenation

Management now: stop escalating respiratory support solely to normalise SpO□. Once adequate arterial oxygenation, ventilation and clinical oxygen delivery are established, wean unnecessary support under monitoring. **I would not give methylene blue for metHb 4.2% alone**; treat clinically significant anaemia/jaundice and continue assessing any genuine recurrent apnoea or hypotonia separately.

The leading diagnosis is **familial haemoglobinopathy with haemolysis and abnormal saturation readings**; the exact variant remains unconfirmed.

80. USER | 08 Oct 2026, 16:16

What is your leading hypothesis? What examinations would you perform?

81. ASSISTANT — progress | 08 Oct 2026, 16:16

I'll distinguish the most likely haemoglobin disorder from the tests needed to identify the exact variant.

82. ASSISTANT | 08 Oct 2026, 16:17

My leading hypothesis is a paternally inherited unstable haemoglobin variant, causing haemolysis and abnormal oxygen-saturation measurements, possibly with reduced oxygen affinity and increased methaemoglobin formation. An Hb M variant is a close alternative; the exact variant cannot yet be named.

This unifies:

- The infant's prolonged jaundice and **Hb 11.5 g/dL**.

- The father's chronic haemolytic anaemia and gallstones.

- Similar low SpO□ in both, with little cardiopulmonary explanation.

- Elevated measured metHb and failure of the infant's SpO□ to respond to respiratory support.

I would not attribute everything to metHb 4.2% alone. Abnormal haemoglobin can also distort pulse-oximetry and co-oximetry readings. A normal electrophoresis does not exclude an unstable variant. Diagnostic series

Priority	Examination	What it would establish
1	**Retrieve the father's original haematology and genetic reports**	May identify the familial variant immediately and allow targeted testing in the infant
2	**Arterial blood gas with simultaneous SpO□ and co-oximetry**, documenting FiO□; specialist laboratory review	Establish arterial oxygenation and assess optical interference. **Venous pO□ 30 mmHg cannot answer this question**

Priority	Examination	What it would establish
3	FBC, reticulocytes, bilirubin fractions, LDH and expert blood film	Confirm and quantify haemolysis; look for polychromasia, bite/blister cells or other diagnostic morphology
4	**Supravital Heinz-body staining and haemoglobin stability tests**—heat/isopropanol	Support an unstable haemoglobin diagnosis; negative tests do not exclude every variant
5	Repeat specialist **HPLC/capillary electrophoresis**, reviewing raw traces; mass spectrometry if available	Detect an overlooked or co-eluting variant and verify the earlier age-inappropriate Hb fractions
6	**Globin-gene sequencing in father and infant**, covering **HBA1, HBA2 and HBB**	Identify the molecular diagnosis and demonstrate familial segregation
7	Reference-laboratory oxygen-dissociation curve/**P50**	Test reduced oxygen affinity: an increased P50 supports it. Interpret with attention to HbF and dyshaemoglobins
8 — if unresolved	Cytochrome-b5 reductase activity and **CYB5R3** testing; broader hereditary-haemolysis investigations	Evaluate enzyme-related methaemoglobinaemia or another inherited red-cell disorder

Stability testing, Heinz-body staining, oxygen-affinity assessment and molecular testing are complementary investigations. Molecular diagnostic guidance

The most decisive examination is identifying the same pathogenic globin variant in father and infant. Meanwhile, establish adequate arterial oxygenation before withdrawing support, and assess any genuine apnoea or persistent hypotonia separately rather than assuming the haemoglobin disorder explains them.

83. USER | 08 Oct 2026, 16:18

What is the difference between a paternally inherited unstable haemoglobin variant and Hb M?

84. ASSISTANT | 08 Oct 2026, 16:18

They are overlapping categories, not mutually exclusive diagnoses. My earlier wording made them sound more separate than they are.

	Unstable haemoglobin	**Hb M**
Main defect	The haemoglobin molecule is structurally unstable and can denature/precipitate	A structural globin change favours or stabilises haem iron in its **oxidised Fe^{3+} state**, producing methaemoglobin
Main consequence	Red-cell damage and **haemolysis**	Reduced functional oxygen-carrying capacity and often **cyanosis/low SpO_2**
Typical findings	Anaemia, reticulocytosis, jaundice, Heinz bodies, sometimes pigment gallstones	Persistent methaemoglobinaemia; saturation measurements may be misleading
Oxygen affinity	May be reduced, increased or relatively normal, depending on the variant	Oxidised haem cannot bind oxygen; effects on the remaining functional haem depend on the variant
Diagnostic tests	Stability tests, Heinz-body staining and globin sequencing	Specialist metHb/Hb analysis and globin sequencing

Some Hb M variants are also unstable and cause haemolysis. Hb M-Saskatoon, for example, can have both properties. Conversely, many unstable haemoglobins are not Hb M variants. Hb M-Saskatoon study

“Paternally inherited” describes inheritance—not a different biochemical disorder. Either an unstable variant or an Hb M variant could be inherited from the father.

For this case, the most accurate working description is **a familial structural haemoglobin variant causing haemolysis and abnormal oxygenation measurements**. Molecular identification will determine whether it is an unstable Hb, an Hb M variant, or both.

85. USER | 09 Oct 2026, 16:58

Export the full chat history (prompts and output) to a pdf-file.